Outcomes of China Free Antiretroviral Treatment Program, 2003 - 2010

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ABSTRACT

HAO ZHU: Outcomes of China Free Antiretroviral Treatment Program, 2003 - 2010
(Under the direction of Sonia Napravnik)

Mortality and morbidity from HIV has dramatically decreased in both high- and low-income countries. However, some patients may not benefit from combination antiretroviral therapy (cART) because of inadequate access to HIV care, including attrition after care initiation. Moreover, prior work has concentrated on internal comparisons of mortality among HIV-infected patients over time.

This study had two specific aims. For the first aim, we described cumulative incidence rates of attrition and identified independent factors predictive of attrition. For the second aim, we evaluated observed mortality rates, excess mortality rates and standardized mortality ratios across calendar years. Factors associated with excess mortality across calendar time were evaluated in Poisson regression models.

For the first aim, we observed a cumulative probability of attrition from cART initiation of 9% at 12 months, 16% at 24 months and 24% at 60 months. Factors were associated with attrition, including younger age, male gender, and being single or divorced. Patients with higher CD4 cell counts were more likely to drop out. The proportion of patients remaining in HIV care increased in more recent calendar years and among patients who initiated modern cART regimens.

For the second aim, we found observed and excess mortality rates in 2003/2004 of 9.5 deaths/100 person-years and 9.1; and in 2008/2009 these decreased to 5.6 and 5.2 respectively. The adjusted excess hazard ratio (eHR) for 2003/2004 in comparison to

2008/2009 was 1.27 (95% confidence interval [95% CI]: 1.11, 1.45). Patients initiating cART at CD4 cell counts <50 cells/μL in comparison to ≥350 cells/μL had an adjusted eHR of 9.92 (95% CI: 8.59, 11.44). Standardized mortality ratio results were consistent with those for excess mortality.

In summary, attrition can lead to premature morbidity and mortality, and possibly affect further transmission of HIV and HIV resistant drug variants. In China effective strategies may include focusing particularly on younger male patients and those with higher CD4 cell counts at therapy initiation. Moreover, notable substantial decreases in excess mortality were observed from 2003 to 2009 in China among HIV-infected patients receiving free cART. However, mortality among HIV-infected patients remained higher than the general Chinese population.

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LIST OF ABBREVIATIONS

HIV	Human immunodeficiency virus
AIDS	Acquired immune deficiency syndrome
STD	Sexually transmitted disease
cART	Combination antiretroviral therapy
WHO	World Health Organization
CDC	Centers for Disease Control
NCAIDS	National Center for AIDS/STD Control and Prevention
NFATP	National Free Antiretroviral Treatment Program
IDU	Injection drug use
MSM	Men who have sex with men
ART-LINC	Antiretroviral Therapy in Lower-Income Countries
ART-CC	Antiretroviral Cohort Collaboration
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
IeDEA	International epidemiologic Databases to Evaluate AIDS
SMR	Standardized mortality ratio
CI	Confidence interval
HR	Hazard ratio
IQR	Interquartile range
CRF	Case report forms
OI	Opportunistic infection
EFV	Efavirenz

NVP	Nevirapine
3TC	Lamivudine
ddI	Didanosine
AZT	Zidovudine
D4T	Stavudine
ALT	alanine aminotransferase

I. SPECIFIC AIMS

Specific Aim 1: To describe and evaluate attrition following combination antiretroviral therapy initiation in China, 2003-2010.

Aim1a: To identify independent risk factors associated with time from cART initiation to attrition. *Hypothesis:* Patients who are younger, male, injecting drug users, receive HIV care at smaller clinics, reside in the western region of China, with lower CD4 cell counts, earlier calendar year of starting cART, fewer symptoms and cART not including lamivudine will be at greater risk of attrition.

Aim1b: To evaluate the effect of calendar year of starting cART on time to attrition. *Hypothesis:* Patients who initiated cART in earlier calendar years will be at greater risk of attrition after adjustment for demographic and clinical characteristics.

Aim 1c: To evaluate the effect of type of health care setting on time to attrition. *Hypothesis:* Patients who initiated cART in central hospitals will be at lower risk of attrition.

Specific Aim 2: To describe and evaluate excess mortality among HIV-infected patients receiving cART in comparison to the general population in China, 2003-2009.

Hypothesis: Patients who are younger, male, injecting drug users, receive HIV care at smaller clinics, reside in the western region of China, with lower CD4 cell counts, earlier calendar year of starting cART, fewer symptoms and cART not including lamivudine will be at greater risk of excess mortality.

II. BACKGROUND

The HIV Epidemic in China

Based on the Chinese Notifiable Cases System, as of the end of October 2007, the cumulative number of HIV-infected persons diagnosed in China was 223,501, of whom 62,838 had an AIDS diagnosis, as of the end of October 2007 [1]. Meanwhile, the official estimation of HIV-infected persons living in China was 700,000 with 20,000 AIDS related deaths observed through the end of 2007 [1]. The major route of transmission has been injection drug use (IDU), which accounts for 39% of infections, followed by former blood donation (19%), heterosexual transmission (18%), receipt of blood products (4%), mother to child transmission (1%) and homosexual transmission (1%). In the rest (18%) the transmission mode is unknown. The proportion of HIV-infected individuals in China who are male is more than twice that of female (71% vs. 29%) [1]. Figure 2.1 illustrates the geographical distribution of HIV accumulative cases in China through the end of 2009.

HIV infection has rapidly grown in China since 1985 when the first case was reported in a foreign tourist. During 1985 to 1989, several cases were reported among patients infected by blood products or aboard [2]. The first indigenous HIV positive patients were reported in 1989 when one outbreak of HIV was found among heroin users in Yunan province, located in the southwest of China near the Golden Triangle border area between China and Myanmar [3-8]. Subsequently, HIV has been identified in the neighboring provinces of Yunan, including Guangxi, Sichuan, Guangdong, along with the drug trafficking routes. During the mid-1990s, HIV positive patients were recognized among

commercial plasma donors, which represented the second outbreak in central provinces of China. As of 1998, all 31 Chinese provinces had reported HIV-infected cases. From 1995 through 2000, the reported number of new HIV cases rose by 30% each year; however, the rate of new diagnoses reached 58% in 2001 because of increased reporting of HIV-infected individuals infected through former blood/plasma donation and continued to rise with the rate reaching 122% in 2003 [3, 4].

According to results from the national sentinel surveillance, the average prevalence of HIV is currently 5% among IDUs living in China, with some blips as high as 50% to 80% in several provinces[3]. The infection rate among blood and blood product recipients was 9% in Henan province in 2004 and similar results were observed in other provinces [2]. Due to ongoing screening of blood and blood products this route of infection is decreasing in China.

The estimated prevalence of HIV infection among China's population is 0.05 % (range 0.04 - 0.07%) [1]. However, based on national sentinel site information, the prevalence of HIV infection among 81 national sentinel sites of STD patients has risen from 26% to 46% between 2003 and 2006 [2]. During the same period, the prevalence of HIV increased from 33% to 44% among 36 national sentinel site of sex workers [2]. Among men who have sex with men (MSM) the prevalence is low, the impact cannot be negligible though [9].

In summary, in China the HIV epidemic continues to grow at a rapid pace, although certain regions and populations are affected more than others.

Chinese national HIV/AIDS surveillance system

The China HIV/AIDS surveillance system developed in three phases [10-12]. In the first phase (before 1995), only passive reported surveillance existed. Cases from local hospitals and centers for diseases control at the county level were reported to provincial and central authorities. Two target populations were specially monitored: foreigners and female sex workers. Few active surveillance activities existed during this first phase except in selected provinces where HIV cases were being reported early. During the second phase (1995-1997), active surveillance was initiated through the HIV/AIDS sentinel surveillance system. This sentinel surveillance system included 42 national HIV sites in 23 provinces specifically focusing on several high risk populations. The third phase (1998-present) added behavioral surveillance surveys (BSS) into the national surveillance system. The BSS applied epidemiology and demography methods to conduct surveys among specific target populations to help project the Chinese HIV epidemic [10-12].

Currently, the Chinese surveillance program is an integrated single comprehensive system which includes the National HIV/AIDS case report system, the National HIV sentinel surveillance system, the National HIV behavioral surveillance system, and some additional specific surveys. The National Center for AIDS/STD Control and Prevention (NCAIDS) has been in charge of the national HIV surveillance system since 2001. To improve the quality and timeliness of HIV data, NCAIDS updated the surveillance system into a web based HIV/AIDS case reporting system, by which the NCAIDS can monitor the HIV/AIDS epidemic even at the daily county level [12].

The central government announced the China Comprehensive AIDS Response program in 2002, which integrated HIV care and treatment and prevention activities. Under

this initiative the National Free Antiretroviral Treatment Program (NFATP) was established and was integrated with the national HIV surveillance system. This new system enrolled HIV-infected patients, initiated them on combination antiretroviral therapy (cART) as indicated, and longitudinally followed patients - frequently in the first three months following cART initiation and then every three months, thereafter. This new system applied the same national identification code as used in the National HIV/AIDS case reported system allowing for linkages between the two systems.

Attrition

Attrition among HIV-infected patients after cART initiation.

It has been well documented that cART suppresses HIV viral replication, lengthens patient's survival and lowers AIDS-related mortality and morbidity in both a number of clinical trials and observational studies since its introduction in 1996 [13-19]. However, the discontinuation of cART, either due to attrition or suboptimal cART adherence, leads to failure of HIV RNA viral suppression, reversal of immune reconstitution [20-23] and potentially greater infectiousness. Therefore, the issue of attrition and the factors associated with attrition have been studied as described below.

Definitions of Attrition: A number of studies describing and evaluating factors associated with attrition after initiation of ART are listed in Table 2.1. Studies adopted a range of time intervals as the definitions for attrition according to the study population, the study design and the accessibility of data. Normally, the definition of attrition could be classified into two categories: one definition of attrition consisted of traced deaths, transfers out to other facilities and untraced contacts (unknown contact) [24], whereas the other

definition included the non-death attrition or untraced contact only [25]. In addition, the definition of attrition applied different time intervals to classify the attrition among the patients. Table 2.1 shows a range of time intervals from more than 6 weeks [26] to the maximum, more than one year, to define the patients as lost to follow-up [27]. The definition with longer interval for attrition allows patients greater opportunity to come back to HIV care. Therefore specificity is likely higher in studies using a longer time interval to define attrition. However, sensitivity could be lower when longer intervals of time are used to define attrition. Therefore, due to differences in the definition and measurement of attrition across different studies results need to be interpreted cautiously particularly when comparing one study to another. Most studies done in both developing and developed income countries have evaluated the status and impact of attrition by actively tracking patients using their contact information such as mailing address or telephone after being identified as lost to care. In contrast, other studies in developing income countries have identified and evaluated attrition by cross-checking with vital registry records [28].

Prevalence of attrition: The prevalence of attrition is heterogeneous from different regions and populations, in part due to the different definitions of attrition used, study designs and analyses, and available sample sizes [29]. In Africa, for example, a systematic review mentioned the proportion of attrition ranged from 20% at 6 months to 40% at 2 years [29]. In addition, the study from Antiretroviral Therapy in Lower-Income Countries (ART-LINC) collaboration reported an overall rate of attrition of 15% during the first year of ART - lower (12%) in settings with active follow up and higher (19%) in settings with no or passive follow up [18]. In summary, across studies, the proportion of attrition after ART initiation

ranged from 2.6% for two years to 32% for three years follow up in low-income countries during studies conducted between 1992 and 2006 (Table 2.1) [30-36].

In contrast, the proportion of attrition was generally lower in developed countries than among developing countries. For example, in one randomized clinical trial in the USA, the percent of attrition was 3% after the first year follow-up in 1988 and the cumulative proportion of attrition was 34% in 1994 after seven years of follow-up [30]. Further, the probability of attrition based on French cohort data was 3% during 6 months follow up [27, 37, 38]. Overall, these numbers were dependent on the study population, study period and definitions used.

Factors related to attrition: Factors associated with attrition among HIV-infected patients receiving cART have been assessed in previous studies and showed differing conclusions. In developing countries, one of the most important reasons for attrition was socioeconomic factors. For instance, Maskew et al reported that the most frequent reason for attrition in a South African cohort was financial concerns [39]. Also, Zachariah et al showed that patients who had to pay for cART were more likely to be lost to care among patients receiving cART in Kenya [40]. Demographic characteristics including age, race and education have been examined for their association with attrition. The majority of studies conducted in developing settings did not find associations between attrition and demographic factors [33, 40-44]. Gender has been associated with attrition in some studies [25, 27, 44] but not all [43] with men both more and less likely to be lost to care in comparison to women. Additionally, most studies in developing countries have also not observed differences in attrition based on the patient's clinical status including CD4 cell count, HIV RNA viral load, the presence of a clinical AIDS diagnosis, or weight [24-26, 28, 31-33, 40-46].

On the other hand, in developed areas of the world demographic factors including younger age, male gender, black race and IDU have been reported to be associated with attrition. The potential explanation for the discordant findings in comparison with developing countries could be due to more power with larger sample sizes, more detailed and precise measurements of study variables, in addition to differences in study populations and care provision practices. Like findings from developing areas, patient clinical factors including CD4 cell count and HIV RNA level did not appear to be associated with attrition in the majority of studies that evaluated these factors in developed areas [27, 30, 34-38, 47, 48].

Effects of attrition among HIV-infected patients initiating cART

How attrition can affect research studies: Attrition, if substantially large enough, can affect results of both randomized clinical trials and observational clinical studies and its effects need to be minimized through both improved study designs and advanced statistical methods [30, 35]. Attrition can bias the validity of analyses among patients initiating cART by introducing a selection bias and decreasing statistical power [49]. Attrition may affect analyses if patients who are lost are not a random sample of patients from the entire study population and, therefore, may have greater or lesser probability of experiencing the event of interest, introducing informative censoring [49].

Patients lost to follow up may be sicker than the rest of the cohort and therefore more likely to die [37]. Studies assessing the impact of attrition on results showed that these analyses may underestimate the risk of mortality due to partial death ascertainment among patients who are lost to HIV care. For example, Macphers and Lawn [26, 27] showed that over 50% of the patients lost to care in a rural South African cohort were deceased. The

ART-LINC study investigators contrasting mortality between developed and developing countries observed a higher rate of attrition in low income settings possibly underestimating the mortality rates in these settings [18].

How attrition can affect clinical care outcomes: In addition to its methodological impact, attrition can also affect HIV clinical care outcomes. Attrition generally and particularly in China means that patients will also discontinue their cART, placing them at higher risk of AIDS and non-AIDS clinical conditions and mortality. The cessation of cART not only affects an individual patient's health, it can also have a detrimental impact on the ongoing HIV epidemic through increased transmission. Specifically, successful cART leads to lower genital tract HIV RNA levels and hence a lower likelihood of HIV transmission [50]. Additionally once a patient is no longer engaged in HIV care, additional secondary prevention, including discussions about transmission prevention are no longer possible. Therefore evaluating attrition, its associated factors, and implementing means to reduce attrition is important for both individual and public health.

Strengths and weaknesses of prior studies:

Many of the prior studies have had a number of strengths. The majority of studies in developing areas and most of the studies in developed areas had larger sample sizes and had observational periods of follow up that were more than one year. Therefore, these studies with sufficient sample size coupled with longer follow-up period yield a proportion of patients with attrition that then provides opportunities to examine potential risk factors for attrition in order to make effective policies and intervention methods. Studies conducted in the developed countries included even more participants than those in developing countries.

In previous studies, a significant proportion of patients lost to care died. Yu et al, [24] reported 50% of patients lost to HIV care were dead and 27% were untraceable. Of the studies listed in Table 2.1, a traced mechanism or active follow up was used in most studies in resource-limited setting and in all studies in developed countries. Using an active tracking system in cases of loss to HIV care can supply details regarding patient outcomes and further identify any risk factors associated with greater risk of loss to care. Also, active tracking mechanisms allow researchers to correct survival analysis estimates with data to account for potential biases arising from differential loss to follow-up [46].

Prior studies of attrition also encountered a number of limitations. First, the generalizability of these studies should be interpreted carefully. Differences in the data sources, the study settings and the definition of attrition applied could lead to heterogeneity of the enrolled subjects even in same country. The studies observed in South Africa, for example, have different conclusions about attrition even though they used the same data sources. Cornell et al used more than 3 months as a cut point for attrition while Lawn et al applied more than 4 weeks. As a result, the proportion of attrition in each study was not similar [26, 41].

Second, the time trend effect of attrition may not be well established although studies included adequate sample size. Regardless of whether the studies were carried out in developing or in developed countries, most have followed patients approximately one year after enrollment. One exception is a clinic trial conducted by Ioannidis et al [30]. They followed up 1,609 patients since 1997 until 2004 and found the proportion of attrition ranged from 3% to 34% during seven years follow up.

Third, the potential risk factors evaluated in prior studies were varied. Generally, the demographic factors such as age, gender and race and the health status of patients such as baseline CD4 cell count, HIV viral load and AIDS status were assessed not only in developing but in developed countries. In contrast, few studies from low income countries have evaluated immigrant issues and social economic factors. However, studies conducted in France found that immigrant status, employment status, homelessness and accessibility of medical care could also impact the retention of patients [27, 37]. Therefore, because the risk factors associated with attrition were examined differently, conclusions conflicted among studies. Further study is necessary to identify factors for attrition.

Lastly, another limitation is the potential for information bias. Prior studies acquired information about the patients mainly through medical records, which may not supply precise or current information. Therefore, the results from prior studies may be biased due to misclassification [27].

In summary, the proposed study (n=67,732) will improve on prior work in a number of ways. Foremost, this study will use a very large national and representative cohort to evaluate attrition, and importantly will be able to rely on up to seven years of follow-up. Additionally, we will be able to evaluate a number of factors that may be independently associated with attrition, including sociodemographic factors including: age, gender, mode of HIV transmission, and geographic residence; as well as clinical factors including: type of HIV care provider, CD4 cell count and baseline symptoms. This information will be important to assessing attrition in the free cART program in China and informing the development of interventions to improve both individual and public health.

Mortality among HIV-infected patients initiating cART

Crude mortality among HIV-infected patients initiating cART

With the introduction of cART, the rates of mortality and morbidity among HIV-infected patients sharply decreased [17-19], although the survival benefits have been disproportionate between developing and developed countries. According to one study conducted in 18 low-income programs by ART-LINC, the mortality at 1 year following ART initiation was estimated at 6.4% [95% confidence interval (CI): 5.1, 7.7] with active follow and 2.3% (95% CI: 1.5, 3.2) with passive follow up [18]. Also, a review of 18 published studies in sub-Saharan Africa between 2002 and 2008 reported mortality rates at 1 year from cART initiation of 8% to 26% [51]. Studies from Latin American and south-east Asia identified mortality rates at one year after starting therapy of 8.3% and 11%, respectively [28, 52]. A study by Zhang et al reported high mortality rates during the first 3 months following cART initiation (22.6 deaths per 100 person-years) and decreasing thereafter among HIV-infected patients initiating cART in China [53].

In industrialized countries, on the other hand, observed morality rates have been lower. The estimated mortality from 12 cohort studies by Antiretroviral Cohort Collaboration (ART-CC) during 1 year was 1.8% (95% CI: 1.5, 2.2) [18]. Also, the crude all-cause death rate reported by ART-CC was 12.1 deaths per 1000 person-years (95% CI: 11.6, 12.7) during 1996 to 2006. Moreover, one analysis based on data from 18 cohorts across Europe and 5 cohorts from North America between 1990 and 2004 reported an overall mortality of 5.2 per 1000 person-years (95% CI: 4.7, 5.7) [54]. Overall, mortality rates in ART programs are higher in developing countries than in developed countries, but are heterogeneous with generally much higher rates in sub-Saharan Africa compared with other regions [51].

Calendar time trends in mortality among cART treated HIV-infected patients

Essentially all studies carried out either in developing or developed countries have observed decreased morbidity and mortality in more recent calendar intervals (Table 2.2), although some issues including the accessibility of potent cART [55-59], difficulties with long-term adherence [60-66] and toxicity or drug resistance [67-71] have impacted the effectiveness of cART, regardless of setting. For instance, a study conducted in Canada found mortality rates decreased from 11.7/100 person-years in calendar years 1984-1996 to 2.4/100 person-years in years 1997-2003 [72]. Similarly, Palella et al documented a drop in mortality rates from 3.79/100 person-years in 1996 to 0.32/100 person-years in 2004 using data from the US [73]. A number of other studies have observed similar findings [73-75] and have also consistently documented longer times to AIDS events and greater survival periods following ART initiation in more recent calendar years [14, 76-84].

Risk factors associated with mortality among cART initiated HIV-infected patients

Risk factors associated with increased mortality following cART initiation are summarized in Table 2.3. In industrial countries, almost all of previous studies found an association between CD4 cell count measured at cART initiation and an increased risk of morbidity and mortality when cART was initiated at lower CD4 cell counts [28, 32, 85-101]. In Europe, one analysis carried out among 14,208 subjects from 15 cohorts, part of the ART-CC, found CD4 cell count to be an important prognostic factor for death among HIV-infected patients [102]. Further evidence of a relationship between baseline CD4 cell count and mortality was provided by two other publications. In one analysis including 15 cohort studies from ART-CC [103], the authors reported patients who initiated cART at CD4 cell count

between 251-350 cell/ul had higher rates of AIDS and death than those who began cART at CD4 cell counts between 351-450 cell/ul (HR 1.28, 95% CI 1.04-1.57). Kitahata et al. also observed improved clinical outcomes when patients initiated cART at higher CD4 cell counts [104]. Similarly, the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) also found an association between CD4 cell count and mortality among patients who received therapy and experienced a virologic failure [105]. Thus, results from studies highlight the association between the CD4 cell count and mortality among HIV-infected patients.

In addition to CD4 cell count, other potential factors for mortality have also been evaluated. For instance, using data from NA-ACCORD, Deeks found that higher HIV RNA levels were associated with a higher relative hazard for mortality compared with that of HIV RNA level less than 10,000 copies/ml after second virologic failure [105]. Similar results of the association between HIV RNA level and mortality were found by other previous studies [102, 106]. Moreover, patients who were infected via injection drug use have been generally observed to be at greater risk of mortality [32, 101, 107-110]. Lower body mass index (BMI) or body weight are more likely to decrease survival time compared with higher baseline BMI or body weight [28, 85, 86, 88, 90, 93, 99, 100]. Advanced age is another risk factor documented by several large-size, prospective cohort studies to be associated with an increased risk of mortality [97, 100]. Other studies have found conflicting results for independent effects on mortality of other demographic factors including gender and race [28, 32, 85-101, 107, 109, 110].

The important protective effect of initiating cART at higher CD4 cell counts has also been observed in resource poor regions of the world. For example, a cohort study was

conducted among 2423 patients receiving ART for up to five years in South Africa by Lawn et al [97]. They found patients with the baseline CD4 cell counts less than 100 cells/ml were more likely to die compared with those patients with the baseline CD4 cell counts at least 100 cells /ml. In this study older age was also associated with a higher risk of mortality, but gender/sex did not seem to affect mortality risk. Another analysis in sub-Saharan Africa using data collected through the International epidemiologic Databases to Evaluate AIDS (IeDEA) project conducted by May et al from 2004 to 2007 observed similar results.[100] specifically, among 11,153 patients who started ART, longer survival was strongly associated with higher baseline CD4 cell count (adjusted hazard ratio 0.21; 95% CI: 0.17, 0.27 for ≥200 cell/ul). Higher mortality was also statistically associated with lower body weight, older age and lower lymphocyte count. However, male gender in this study was associated with greater mortality. Lawn et al reported that patients with HIV RNA levels of more than 400 copies/ml after cART imitation were more likely to die (relative risk 2.06; 95% CI: 1.37, 3.09) [97]. May et al reported patients with advanced clinic stage were 2.96 times more likely to die than patients without advanced disease [100].

In brief, patients who are older, have lower CD4 counts, higher HIV RNA levels, advanced clinical stage, lower body weight, and lower lymphocyte count have been observed to be consistently at greater risk of mortality. However patients' race and gender do not seem to be consistently associated with mortality.

Excess mortality of HIV-infected patients who initiated cART

An alternative to evaluating mortality among HIV-infected individuals is to assess mortality among HIV-infected individuals in comparison to HIV-uninfected individuals.

Although a prospective cohort study including both HIV-infected and uninfected individuals would be ideal, it is possible to use readily available mortality rate data that is stratified by sex, age group and calendar year to compare the expected mortality to that which is observed. The observed mortality consists of expected and excess mortality (e.g. the mortality related to HIV-infection) [111]. Two possibilities for estimating excess mortality include the excess mortality rate (absolute scale) and standardized mortality ratio (SMR) (relative scale). The excess mortality is the difference between the mortality of HIV-infected patients who initiated cART and the mortality in general population matched for age group, sex and calendar year. The SMR is ratio of observed survival to the expected survival generated from the national general population after adjusting age, sex and calendar year to study population. Advantages of this approach include, an estimate of excess mortality due to HIV-infection (biologic factors as well as contextual factors) in comparison to the mortality observed in the general population, and thus, do not need the information for individual's cause death. It is important to match on age group and sex in these analyses [112].

Excess mortality analyses using data on population mortality rates have been used extensively in cancer studies for several years [113]. In HIV a number of studies have evaluated excess mortality in Europe and Africa. One study has been conducted by Bhaskaran et al by using data from the Concerted Action on Seroconversion to AIDS and Death in Europe [114]. They found excess mortality decreased from 41/1000 person-years before 1996 to 6/1000 person-years in 2004-2006 and concluded the mortality rates for HIV-infected patients have become closer to mortality in general population after introduction of cART [114]. This study is important because it includes information on timing of HIV-infection in addition to timing of cART initiation. Brinkof has also showed that the mortality

of HIV-infected patients who initiated cART were still higher compared with that in general population in Sub-Saharan African, although excess mortality in some patient groups was improving in comparison to the general population [115]. Keiser and Jaggy also evaluated excess mortality among HIV-infected patients in comparison to the general Swiss population [116, 117].

In summary, notwithstanding modern cART, HIV-infected individuals continue to experience excess mortality in comparison to the general population even among individuals who successfully respond to cART [118, 119]. Using excess mortality analyses is critical to provide policy makers with accurate information to evaluate the effect of cART and monitor the change of mortality among HIV-infected patients at a general population level.

Decentralization of cART among HIV-infected patients

In resource rich areas of the world, the majority of patients with HIV-infection are followed by clinicians with specialized HIV treatment knowledge and with access to relatively sophisticated and expensive laboratory and other types of monitoring [120]. However this level of HIV care is difficult to provide in resource poor areas of the world because of scarce resource and lack of HIV experienced clinicians. On the other hand, the majority of people infected with HIV live in developing countries. Therefore, WHO has strongly supported cART provision even in the most resource deprived areas of the world [121]. Previous studies have evaluated how best to provide HIV care and ART in developing countries. One study which included 5719 HIV-infected patients in South Africa evaluated a decentralized model of cART provision in rural areas [122]. The study found that the overall mortality rate was high but was similar to mortality rates observed in more urban areas and in

more specialized programs also in South Africa. Notably, the rate of attrition was relatively lower in this rural study population in comparison to urban areas. Other studies also conducted in South Africa have observed similar success in delivery of HIV care and cART in rural and impoverished areas [123]. As prior studies showed, attrition was lower in these rural clinics than in hospital based HIV clinics [123]. Comparable results have also been reported from neighborhood countries [124, 125].

In summary although HIV care and cART provision can and are successfully provided throughout resource limited settings additional work is needed to identify program structures that lead to the best patient clinical outcomes.

Strengths and weaknesses of prior studies:

A large number of studies have evaluated mortality among HIV-infected individuals receiving cART across many calendar years, areas of the world, and program settings, with many of these studies of exceptionally high quality. Many prior studies have had large sample sizes leading to more power and precision. Some studies in Table 2.2 had more than 1,000 subjects and some had more than 10,000 subjects. These relatively large sample sizes have allowed investigators to evaluate mortality in specific subgroups of patients and across calendar time. Also the wide distribution of studies globally has allowed investigators to draw conclusions that are often generalizable to many HIV-infected individuals receiving HIV care and cART around the globe.

On the other hand, some prior studies have also had certain limitations. First, several studies lacked information on potential confounders and therefore they were not able to completely exclude the possibility that some of their findings may be due to unmeasured

confounding. For example, Schewarcz et al acknowledged that their study could not adjust for HIV RNA levels or systemic symptoms, which may impact patients' survival time [79]. Also, Nash et al mentioned they did not add specific factors including health insurance, access to treatment and health behavior factors into their analysis [83]. Secondly, in some cases studies were affected by high mortality rates among patients who were lost to HIV care. As mentioned by Couzgou [80], 12% of their study patients who were lost to care were younger, infected by heterosexual activity and diagnosed with tuberculosis, all factors related to shorter survival time in this cohort. These authors also noted that their findings may be affected by survival bias since only patients who survived long enough to initiate cART were included in their study (as is common among many studies evaluating HIV related mortality) [80].

The present study builds on prior work in a number of ways. First this is one of the largest cohorts of HIV-infected individuals internationally, and the only one of its size and scope in China. To date no analyses have focused specifically on retention and attrition among the large number of HIV-infected individuals receiving free cART through NFATP. Understanding who becomes lost to HIV care and the scope of this problem in China is important to intervene to improve both individual and public health in a country where HIV infection continues to spread rapidly. Additionally evaluating mortality among HIV-infected patients receiving cART in China across calendar years and in comparison to the general Chinese population will provide important data for policy makers.

Table 2.1 Rates of attrition and risk factors among HIV-infected patients initiating cART

First Author	Year	Region	N	Definition of attrition	Active Follow up	Ratio/Rate	Risk factors for attrition
Geng [46]	2009	Uganda	3,628	6-month absent from clinic	Yes	22% during 3.5 yrs	N/A
Cornell [41]	2009	South Africa	2,196	Patients who have start ART but were absent more than 3months	N/A	6% during 1yr	1)Lower incoming was associated with attrition; 2)Age, gender, baseline CD4, VL not associated; 3)Not others were tested
Macpherson [25]	2008	South Africa	1,353	Patients who could not be traced and not returned to clinic during 24 months. (Non-death attrition)	Yes	2.6% during 2yrs	1)male, lower weight, lower baseline CD4, WHO stage 3-4 were associated with attrition 2) Not others were tested
Kaplan[42]	2008	South Africa	1,677	Patients with ART who not attended the clinic >12 weeks	No	32% during 3 yrs	1)Pregnancy, young age were associated with attrition 2) WHO stage, baseline CD4, VL not associated; 3)Not others were tested
Dalal [45]	2008	South Africa	1,631	Receiving ART and disappear > 6weeks	Yes	16.4% during 1yr	N/A
Lawn [26]	2006	South Africa	927	Receiving ART who were>4 weeks late for scheduled clinic visit	Yes	11.9% during 3yrs	1) baseline CD4 were not associated with attrition 2) Not others were tested
Yu [24]	2007	Malawi	5,009	Patients who have not seen in clinic for 3 consecutive months	Yes	5.1%	N/A
Fetzer [126]	2009	Malawi	258	N/A	No	12%	N/A

Table 2.1 Rates of attrition and risk factors among HIV-infected patients initiating cART (continued)

First Author	Year	Region	N	Definition of attrition	Active Follow up	Ratio/Rate	Risk factors for attrition
Zachariah [40]	2007	Kenya	435	Receiving ART and disappear >2 months	No	47.2 and 20.5 per 100pys for payment and free cohort	1)Payment for ART was associated with attrition 2) Gender, age, Marital status and baseline CD4 were not associated 3) Not others were tested
Karcher [43]	2007	Kenya	159	Receiving ART and disappear within 4 months after a scheduled appointment	Yes	43.2 per 100pys	1) Adherence<2m was associated with attrition 2) Age, gender, race, education, baseline CD4, pregnancy were not associated with attrition. 3) Not others were tested
Lowrance [44]	2009	Rwanda	3,194	Patients who have not been seen at the clinic for any reason for >90 days	No	3.1% at 6M;4.9% at 12M	1)Man, lower Baseline CD4 and lower body weight were associated with attrition; 2)Age not associated with attrition; 3) No other factors were tested
Toure [33]	2008	West Africa	10,211	Last contact with program>3 months or >6months while do not know to be dead or transferred out	No	Prob. 0.21 in 18 months	1)man, experienced clinical, low hemoglobin were associated with attrition; 2)Age, baseline CD4 counts were not associated with attrition; 3) No other factors were tested
Nacher [31]	2006	French Guiana	1,213	Permanent interruption	No	17.2 per 100 pys	1)age<40 and lower baseline CD4 were associated with attrition; 2) gender and baseline CD4 were not associated with attrition 3) No other factors were tested
Pacheco [32]	2009	Brazil	1,538	N/A	N/A	2.4 per 100pys	N/A

Table 2.1 Rates of attrition and risk factors among HIV-infected patients initiating cART (continued)

First Author	Year	Region	N	Definition of attrition	Active Follow up	Ratio/Rate	Risk factors for attrition
Chasombat [28]	2009	Thailand	81,960	Patients who were late for clinic visit >3 months	No	8.8%	N/A
Ndiaye [38]	2009	French	1,007	N/A	Yes	3.5 per 100pys	1)age<30, IDU, no phone number, no primary care, higher baseline CD4, lower recent CD4 and no cART were associated with attrition 2) No other factors were tested
Mocroft [37]	2008	French	12,304	No follow up visit and no CD4 , no VL and no death	Yes	3.72 per100 pys (3.58-3.86)	1)male, younger age, IDU, no ART and recent CD4 were associated with attrition 2)race was not associated with attrition 3) No others were tested
Lebouche [27]	2006	French	1,756	Not attended our clinic or another clinic >1year	Yes	4.3 per 100 pys	1) age<30y, IDU, homeless, ART <1997, lack of primary care and AIDS in enrollment and psychiatric disease history were associated with attrition 2) gender, baseline CD4, unemployment were not associated with attrition
Lanoy [35]	2006	French	34,835	Patients who had no further visit during 12 months after their last visit in 1999	Yes	8.5% overall ; 16.8% <1 yr vs. 7.1%> 1yr diagnosed	Diagnosed recently: Non-AIDS immigrant and High VL were associated with attrition but not lower recent CD4; Diagnosed >1 year: young age, immigrant, IDU were associated with while lower recent CD4, High VL not;
Haddow [34]	2003	UK	94	Patients who enrolled in our HIV clinic within 15 months but not received 12 months	N/A	N/A	1)Age was associated with attrition 2) gender, race, AIDS stage were not associated 3) no others were tested

Table 2.1 Rates of attrition and risk factors among HIV-infected patients initiating cART (continued)

First Author	Year	Region	N	Definition of attrition	Active Follow up	Ratio/Rate	Risk factors for attrition
Brown [47]	2006	USA	1,052	patient who missed all study visits and could not be contacted for 12 consecutive months, who had not died and who did not re-enter the study at a later date	Yes	3 per 100 pys	1)Younger age, lower education level, unemployed, bad baseline health status, heterosexual contact were associated with attrition; 2)gender and race were not associated 3) no others were tested
Yehia [36]	2008	USA	13,833	Missing follow up for 6 months or 1 years	Yes	15% per year (5-25%)	N/A
Ioannidis [30]	1997	USA	1,609	N/A	Yes	3%-34% during 7 years	1)Young age, race, IDU were associated with attrition; 2) baseline CD4 was not associated 3) no others were tested
Coleman [48]	2007	USA	495	N/A	Yes	14% in 4yrs	1)minority, insurance net, no medical social work, recent CD4 and higher VL were associated with attrition 2) age were not associated with attrition 3)no others were tested
Maskew [39]	2007	South Africa	5,849	Missing 2 months	Yes	2.6%	1) financial

Table 2.2 Trend of mortality among HIV-infected patients initiating ART

Authors	Years for study	Region (study)	N	AIDS Diagnosis	Survival Trend
Yang [127]	1984-2005	Taiwan	10,162	N	Decreased mortality:10.2/100 pys in the pre-HAART;6.5&3.7/100pys in the early and late HAART
Krentz [72]	1984-2003	Canada	N/A	N	Decreased mortality:11.7/100pys in pre-HAART decreased to 2.4 /100pys in the HAART
Mocroft [19]	1994-2002	EuroSIDA	9803	N	Decreased the risk of all deaths: 0.66RH in the late-HAART era, while 1.29 HR in the pre-HAART
CASCADE [128]	1986-1998	CASCADE	5646	N	Decreased the risk of deaths:64% compared with pre-HAART
Maria [129]	1980-1997	Italy	1535	N	Decreased the risk of deaths: 0.54 RH in 1997 compared with that in the 1991.
Correl [130]	1990-1997	Australia	346	N	Decreased the risk of death: 0.20 RH in early HAART compared with pre-HAART
Detels [13]	1984-1997	USA	536	N	Decreased the risk of death:0.62 during HAART compared with pre-HAART(monotherapy)
Murphy [131]	1995-1999	VATS	528	N	Decreased mortality: decreased from 0.88 event/py to 0.26 event/py during taking HAART
Palella [16]	1994-1997	USA	1255	N	Decreased mortality : decreased from 29.4 /100pys to 8.8 /100pys
Vittinghoff [132]	NA	San Francisco	622	N	Decreased the risk of death: 0.45 during 1996 calendar year
Schwarcz [79]	1987-1996	San Francisco	15,271	Y	Median survival time increased
Pezzotti [78]	1985-1997	Italy	1,683	Y	Median survival time increased from 2.9 in before diagnosed in1987 to 15 months diagnosed in 1996-1997
McNaghten [77]	1990-1997	USA	19,565	Y	Median survival time increased
Lee [76]	1984-1997	USA	394,705	Y	Median survival time increased from 11 months for 1984 diagnoses to 46 months for 1995 diagnoses.

Table 2.2 Trend of mortality among HIV-infected patients initiating ART (continued)

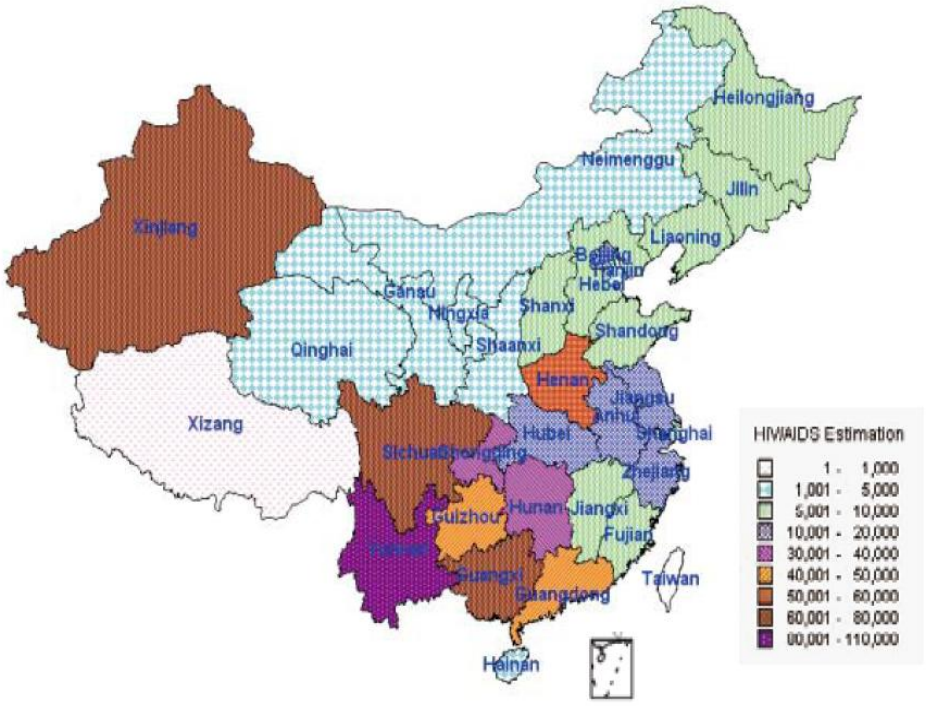
Authors	Years for study	Region (study)	N	AIDS Diagnosis	Survival Trend
Gange [14]	1994-1999	USA	1,691	Y	Decreased mortality: decreased from19.47/100pys during 1995 to 6.32/100pys
Fordyce [82]	1990-2001	NYC, USA	79,878	Y	Cumulative survival increased from 43% diagnosed during 1990-95 to 76% during 1996-98
Dore [81]	1993-2000	Australia	4,351	Y	Median survival time increased from 19.6 months before HAART to 39.6 months
Nash [83]	1993-2001	NYC, USA	93,585	Y	Death rates substantially decreased.
Del Amo [133]	1985-2003	Spain	585	N	Decreased the risk of death: decreased 72% during 1997-2000 and 83% during 2001-03 compared with 1993-96
Smit [84]	1982-2000	Netherlands	2,305	Y	More than 10 times of AIDS death after introduction HAART.
Couzigou [80]	1994-2002	France	4,158	Y	Decreased mortality.
Perez-Hoyos [74]	1996-2003	GEMES	1,129	N	Decreased the risk of death: 0.55 HR during 1998-99 and 0.40 HR during 2000-2003.
Palella [73]	1996-2004	HOPS	6,945	Y	Decreased death AIDS-related: decreased from 3.79/100 pys in 1996 to 0.32/100pys in 2004
CASCADE [75]	Pre1997-2001	CASCADE	7,740	N	Decreased the risk of death: 0.47HR in 1997 and 0.16 in 2001

Table 2.3 Risk factors for mortality among HIV-infected patients initiating cART

Author	N	Age	Gender	Race	Baseline weight /BMI	Baseline CD4	Baseline Hemoglobin	HIV exposure
Sieleunou [85]	1,187	-	Y	-	Y	Y	Y	-
Etard [86]	404	N	N	-	Y	Y	Y	-
Zachariah [99]	2,316	N	Y	-	Y	Y	-	-
Johannessen [88]	320	N	Y	-	Y	-	Y	-
Bussmann [89]	633	-	-	-	-	Y	Y	-
Severe [90]	910	-	Y	-	Y	Y	-	-
Weidle [91]	254	-	-	-	-	Y	-	-
Coetzee [92]	287	N	Y	-	-	Y	-	-
Chasombat [28]	58,008	Y	Y	-	Y	Y	-	-
Pacheco [32]	1,538	N	Y	-	-	Y	-	Y
Stringer [93]	21,755	N	Y	-	Y	Y	Y	
Silverberg [94]	4,686	N	N	N	-	Y	-	-
Taiwo [95]	122	-	-	-	-	Y	-	-
Ojikutu [96]	309	N	N	-		Y	-	-
Lawn [97]	2,423	Y	N	-	-	Y	-	-
Russell [98]	1,350	N	N	-	-	Y	Y	-
Zachariah [99]	1,507	N	N	-	Y	Y	-	-
May [100]	10,331	Y	Y	-	Y	Y	-	-
Cook [108]	1,690	-	-	Y	-	-	-	Y
Colebunder [107]	1,366	N	N	-	-	-	-	Y
Hsu [109]	8,410	Y	N	Y	-	-	-	Y
Keruly [110]	959	Y	-	N	-	-	-	Y
Pezzotti [101]	3,169	N	N	-	-	Y	-	Y
ART-LINC & ART-CC[18]	27,027	N	Y	-	-	Y	-	-
ART-CC [102]	14,208	-	-	-	-	Y	-	-

*Note: “Y” stands for statistical significance; “N” stands for no statistical significance; “-” represents no investigation for that study.

Figure 2.1 Geographic Distribution of Cumulative HIV Cases Reported in China through 2009



III. METHODS

Study Population

The patients for this dissertation are from a nationwide, ongoing, prospective study, NFATP, through which patients with HIV in China have been receiving free antiretroviral therapy since the end of 2002 [134]. The NFATP was established by the Division of Treatment and Care in the NCAIDS, Chinese Center for Disease Prevention and Control in response to the HIV epidemic in China.

All individuals receiving cART as part of the NFATP between 1 January 2003 and 31 December 2010 (n=79,750) were eligible for this study. According to the first edition of China Free ART Manual, NFATP enrolled HIV-infected patients age 18 years or greater, with CD4 cell counts less than 200 cells/ul, or WHO stage III or IV disease. At the beginning of 2008, the criteria for CD4 cell count was extended to include anyone with a CD4 less than 350 cells/ul in accordance with WHO guidelines [135]. Previous studies have reported on the baseline characteristics and clinical outcomes among patients with HIV who enrolled in this cohort [53]. In brief, as of August 2008, the study subjects were 42% female, 82% rural and 75% married. The median age at enrollment was 38 years (Interquartile range [IQR] 33 to 46). The median weight was 53 kg for females and 59 kg for males. The main transmission mode was through blood or plasma donation or transfusion (53%). The median baseline CD4 cell count was 118 cells/mL (IQR: 37 - 203) and median hemoglobin level was 12.0 mg/L (IQR:11.0 - 14.0) [53].

Data Collection

Detailed descriptions relevant to the administration, procedures and methods for the NFATP program have been published [134, 136, 137]. The program uses standardized case report forms (CRF) including initial patient assessment, treatment follow-up, treatment regimen change, treatment withdrawal and transfer for each patient visit. Information from CRFs was faxed to NFATP via DataFax (clinical DataFax System Inc., Hamilton, ON, Canada). At the visit when patients start ART, the standardized forms for initial patient assessment is completed. Subsequent follow up visits are arranged at approximately 0.5, 1, 2, 3 months and once every 3 months, thereafter, and the CRF for treatment follow-up is completed during these visits by health providers. When the patients discontinue ART due to, adverse events, or are considered lost to follow-up, transfer to other clinic, or die, the CRF for treatment withdrawal is filled out. The information from these forms provide demographic information, laboratory test results, clinical symptoms and signs and self-reported adherence [134]. Each form faxed is checked twice by the database administrators for discrepant logic errors and missing data. In 2010, a web-enabled electronic data collection system was implemented, which includes the same information as was previously faxed.

The provision of free ART in China includes multiple levels of the health care delivery system, each of which plays different roles in the process of providing treatment to each patient. ART provision is at the county level while routine follow-up, monitoring and care are provided at a village or township level. In addition, clinicians at the county and prefecture level are responsible for diagnosing adverse events, opportunistic infections (OI) and other HIV and ART complications. Provincial and national level health facilities act as

consultative referral centers. All the health workers and clinicians in charge of patients receiving ART are trained by their own provincial centers for disease control (CDC) branch.

Information on death, including reason and date of death, is available through the NFATP treatment withdrawal forms. These forms are also completed by local health workers and sent to central NFATP offices by DataFax (Clinical DataFax Systems, Hamilton, Ontario, Canada). Forms were completed on all patients known to have died at the local level through passive surveillance. Mortality data for the general Chinese population was obtained from *China Health Statistic Year Book 2004* to *2010*.

Measurements and Statistical Analyses for Aim 1

Specific AIM 1: To describe and evaluate attrition following cART initiation in China, 2003-2010.

Identification of attrition**:** Attrition was defined as not having a visit for at least 210 days. This is approximately seven months, which allows leniency for those who miss a standard three-month NFATP visit but are seen within four weeks of the following scheduled NFATP visit. Moreover, this seven month definition is roughly similar to the definition of six months used in prior studies [46, 138]. (Note: if patients miss a scheduled appointment, CDC health workers or physicians who are in charge of the treatment try to contact the patients by telephone or visit the address left by patients.)

Covariates: All information about the outcome variable and covariates were obtained from the CRFs completed by local health workers (Table 3.1). The factors measured at baseline included age, gender, marital status, HIV exposure category, type of health care setting (general hospital, infectious diseases hospital, centers for diseases control clinic,

health care center at township level, village clinic and prison hospital) region (eastern, central and western region), calendar year of cART initiation, CD4 cell count, alanine aminotransferase and hemoglobin level. Baseline symptoms included on the CRF included fever, cough, sputum production, dyspnea, chest pain, night sweat, diarrhea, nausea, projectile vomiting, headache, declining vision, blurred vision, rash, thrush, oral hairy leukoplakia, and lymphadenopathy. For this study, baseline symptom severity was defined by counting the number of symptoms present at baseline. The initial therapy regimens consisted of zidovudine(AZT)/ stavudine (d4T) + didanosine (ddI)+ nevirapine (NVP) between 2003 and 2005. After 2005, the initial regimens were gradually replaced with AZT/d4T+ lamivudine (3TC) + NVP. In this study, we also evaluated the initial cART regimen by classifying regimens based on whether or not they included 3TC.

Statistical Analysis:

We first described the study population based on the following demographic and clinical characteristics measured at baseline (time of cART initiation): age, gender, HIV exposure category, marriage status, type of health care setting, region, CD4 cell count, weight, hemoglobin, alanine aminotransferase, symptom category, initial cART regimen and calendar year of starting cART. We described the overall time to the first attrition event among all patients. Then we will use Kaplan-Meier product limit methods to assess the effect of each factor of interest on time to attrition. We used the log-rank test to compare curves. Cox proportional hazard models were used to estimate unadjusted and adjusted hazard ratios with 95% confidence interval. The proportional hazard assumption was evaluated by a plot of log (-log survival) versus log time. We also fit adjusted Kaplan-Meier curves as indicated.

Aim 1a: To identify independent risk factors associated with time from cART initiation to attrition**.**

For Aim 1a we used a predictive analysis strategy to identify independent predictors of attrition. Based on the bivariable analyses, we identified factors predictive of the outcome with a p-value<0.2. These factors were entered into a full model. Backward elimination was used to remove covariates. The final model only included factors independently predictive of the outcome defined as a p-value<0.05. Given the relationship between type of antiretroviral therapy available through NFATP and calendar year of starting cART, we explored the relationship between type of therapy and attrition in models stratified by calendar year of cART initiation. As a sensitivity analysis we administratively censored follow-up time at 12 and 24 months following cART initiation rather than at 31 December 2010. All hypothesis testing was 2-sided, with α level of 0.05.

Aim1b and 1c: To evaluate (1b) the effect of calendar year of starting cART (1c) the effect of type of health care setting on time to attrition.

For Aim 1b we specifically evaluated the effect of calendar year of starting cART on time to attrition. The methods were analogous to those in Aim 1a, except we fit a traditional epidemiologic model. In these analyses we assessed for effect measure modification by the likelihood ratio test, and confounders were identified using a change-in estimate of 10%. The analyses for Aim 1c were the same as those for Aim 1b, except the main exposure of interest was the type of health care setting where the patient received their HIV care.

Specific Aim 2: To describe and evaluate excess mortality among HIV-infected patients receiving cART in comparison to the general population in China, 2003-2009.

Identification of excess mortality: Excess mortality was defined as the difference in mortality rates between HIV-infected patients in NFATP and people from the general population in China, after adjusting for age, sex and calendar year. 1) All patients recorded as deceased in NFATP from 2003 to 2009 were included in this analysis as the number of observed deaths. The time to death was calculated as the time from cART initiation until death. Patients were right censored at the date of death or 31 December 2009, whichever occured first. The origin of the analysis was the start of cART for each patient. (Note: patients who were not eligible to initiate cART treatment were not included in NFATP). 2) The expected number of deaths was calculated by using the mortality rates of the general population in China, which were stratified by age, sex, area of residence and calendar year and were comparable to this study population. A previous study in China showed that mortality rates in NFATP were greatest during the first 3 months after cART initiation with a mortality rate of 22.6/100 person-year during this period and then decreasing to 4/100 person-years after 6 months; with the same rates during the subsequent 4 years [53]. Figure 3.1 demonstrates the mortality trend for up to 60 months following treatment initiation.

Covariates: Factors measured at baseline included age, gender, HIV exposure category, type of health care setting, and CD4 count at enrollment. Also, baseline symptom severity was defined by counting the number of symptoms present at baseline as described in Aim 1. The initial regimen categories used were the same as those described for Aim 1. The calendar period was categorized as 2003/2004, 2005-2007 and 2008/2009. This categorization was chosen to: minimize heterogeneity within groups; correspond with major therapeutic changes across calendar time; and preserve adequate sample sizes within strata.

Statistical Analyses:

We described the HIV-infected study population receiving cART across calendar periods, including demographic factors, clinical characteristics at cART initiation, and duration of follow-up.

We calculated the observed deaths, person-years of follow-up and the overall mortality rate and 95% CI by calendar periods. The overall mortality rate was calculated as the observed number of deaths divided by person-time in each calendar year and reported per 1000 person-years. We then calculated the expected deaths per calendar year. We created a hypothetical cohort of HIV-uninfected individuals matched to the study population on age, sex, area of residence and calendar year of follow-up. To this hypothetical cohort we applied the general Chinese population mortality rates to estimate expected deaths. Expected number of deaths was calculated by applying annual probability of death from the general Chinese population to the study population considering individuals to be at risk until their actual date of death or censoring.

Excess deaths were calculated by subtracting the number of expected deaths from the observed deaths. Excess mortality rates per calendar year of follow-up were estimated taking the excess deaths in each calendar year and dividing by person-years of follow-up. Excess mortality rates here represent the difference between the observed mortality rates of HIV-infected patients in the study population and the expected mortality rates had these patients experienced the mortality rate of the general Chinese population based on their age, sex and calendar year of follow-up. We also calculated standardized mortality ratios (SMR). These were calculated as the ratio of the number of observed deaths to the number of expected

deaths, and the 95% confidence intervals were calculated. These were calculated stratified by calendar year, and demographic and clinical characteristics.

Multivariable analyses of excess mortality were fit using Poisson models [111]. In this relative survival model, the observed number of deaths in each patient stratum was modeled with a Poisson process and we used the expected number of deaths in each stratum as an offset. Time was categorized in one year increments from cART initiation, assuming a piecewise constant hazard within each year after starting cART. Excess hazard ratios (eHRs) and associated 95% CIs were obtained as the antilog of the coefficient from this relative survival model. We examined changes in relative survival across calendar time adjusting for age, sex, HIV-exposure category, CD4 count, initial cART regimen, type of health care setting and area of residence.

Power Calculation

Given this study relied on existing data we calculated power that each aim of this study would have. We assumed at most a total sample size of 79,750, corresponding to the maximum number of patients who received free cART through NFATP between 2003 and 2009. For all power calculations we used a two-sided test with a 0.05 significance level.

First, to illustrate the power available to evaluate risk factors associated with time to attrition, we used IDU as an example. We used a log-rank test to test for a statistically significant difference between the two survival curves comparing patients exposed to HIV through IDU versus patients exposed through all other transmission categories. We varied the proportion of the study population with IDU from 10% to 30%. We then calculated the expected power for a range of possible hazard ratios (Table 3.2). For example, with 30% of

the study population with IDU, this study has over 80% power to detect a hazard ratio comparing IDU to non-IDU patients of time to attrition of at least 1.25. In comparison we will have over 80% power to detect a hazard ratio of at least 1.4 even if less than 10% of the study population was infected via IDU.

Next, for the evaluation of factors associated with mortality, the index group or reference group was defined based on year of initiation of ART. We used calendar year 2003 as the reference group compared with 2004. We then ranged the expected hazard ratios and calculated expected power (Table 3.3). For example, with 25% of patients receiving cART in 2003, we would have over 80% power to detect a hazard ratio of at least 1.2. Table 3.3 lists the power expected based on varying the expected hazard ratios between two calendar years for one year follow up. Again, our study has enough power to detect even relatively small differences in mortality rates across calendar years.

Human Subjects

This study was a secondary data analysis project and had no direct contact with human subjects. Written informed consent was obtained from the subjects when they accepted treatment and care under NFATP run by the Division of Treatment and Care in the National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention (NCAIDS/CCDC). This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill. The data used for this study did not include any personal identifiers and therefore, the risk to breach of patient confidentiality was minimal. The data were stored on one computer with an encrypted hard disk drive. All other data, electronic and original paper version, are only available to NFATP staff in China.

Table 3.1 Variables list

Variables	Variable Description	Type
Outcome variables (Aim1)		
Time to attrition	Time from initiating cART to attrition which is defined as any patient with HIV infection initiating cART who has the duration more than or equal to 210 days since a scheduled visit.	Continuous
Outcome variables(Aim2)		
Number of excess death	Number of excess death calculated by number of observed death minus number of expected death	Continuous
Covariates		
Age	Age during the enrollment	Continuous
Gender	Gender [0=male, 1=female]	Binary
Marital status	Marital status [0=single, 1=married, 2=divorced,3= widowed]	Categorical
HIV exposure group	HIV exposure group [1=blood or plasma, 2=IDU, 3=MSM, 4=Heterosexual, 5=MTC, 9=unknown.	Categorical
Type of health care settings	Type of health care setting [1=Comprehensive hospitals, 2= Infectious-disease hospitals, 3=Centers for diseases control, 4= township hospital, 5=Clinics in village, 6=others]	Categorical
Baseline symptom categories	Numbers of symptoms appearance during enrollment [0=none,1=1 type, 2=2-3types,3=4-5types	Categorical
CD4 cell count	CD4 cell count measured at enrollment	Continuous
Hemoglobin count	Hemoglobin count measured at enrollment	Continuous
Alanine aminotransferase	Alanine aminotransferase measured at enrollment	Continuous
Body weight	Body weight measured at enrollment	Continuous
Calendar year to initiate cART	Calendar year when patients initiated cART	Categorical
Initial regimens	The initiation of regimens [0=3TC based regimens, 1=Non-3TC based regimens]	Binary

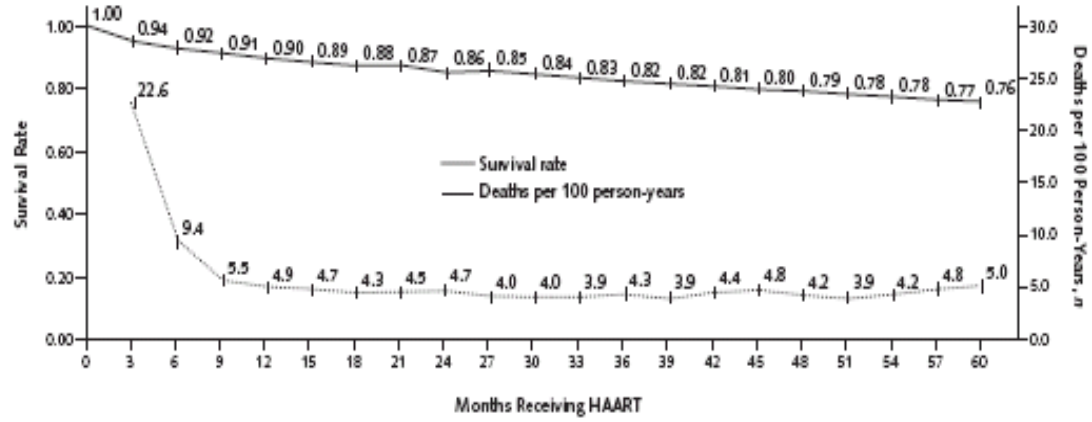
Table 3.2 Power calculated by assumed Hazard ratios of attrition among the index group and the reference group.

Proportion Exposed	Hazard ratios	Power obtained
10%	1.10	11%
	1.20	31%
	1.30	58%
	1.40	82%
	1.50	95%
	1.60	99%
20%	1.10	15%
	1.20	44%
	1.25	60%
	1.30	76%
	1.40	94%
	1.50	99%
30%	1.10	21%
	1.15	40%
	1.20	61%
	1.25	80%
	1.30	91%
	1.35	97%

Table 3.3 Power calculated by assumed mortality rates among the index group and the reference group.

Proportion Exposed	Hazard ratios	Power obtained
20%	1.05	10%
	1.10	27%
	1.15	51%
	1.20	75%
	1.25	91%
	1.30	98%
25%	1.05	11%
	1.10	30%
	1.15	57%
	1.20	81%
	1.25	94%
	1.30	99%
30%	1.05	14%
	1.10	39%
	1.13	58%
	1.15	70%
	1.20	91%
	1.25	98%

Figure 3.1 Mortality rate per 3-months interval among HIV-infected patients receiving cART from June 2002 to August 2008 in China



Entered Interval, n	48785	39403	35378	32227	29175	26278	23891	21805	19802	17789	16136	14351	12693	10810	9294	7263	5394	4119	3020	2178
Censored during Interval, n	6887	3150	2684	2677	2570	2118	1832	1760	1824	1483	1635	1513	1768	1406	1932	1803	1229	1062	811	957
Deaths during Interval, n	2495	875	467	375	327	269	254	243	189	170	150	145	115	110	99	66	46	37	31	21

IV. ATTRITION AMONG HUMAN IMMUNODEFICIENCY VIRUS (HIV)-INFECTED PATIENTS INITIATING ANTIRETROVIRAL THERAPY IN CHINA, 2003 – 2010

Introduction

Local, national and international efforts have strived to make combination antiretroviral therapy (cART) available to patients with human immunodeficiency virus (HIV) around the globe, including China [100, 120, 139]. With these efforts and the increasing effectiveness of provided cART, mortality and morbidity from HIV has dramatically decreased in high- and low-income areas of the world [17, 18, 53]. However, some patients may not benefit from cART because of inadequate access to HIV care, including attrition after care initiation [37, 39, 140]. Estimates of attrition depend in large part on the definition of attrition used, the location and nature of the study population, and other study characteristics [25, 28, 35, 43].

Among HIV-infected patients initiating cART living in high-income areas of the world, attrition rates can be as low as 5% during the first year of treatment [18]. Studies conducted among patients living in low-income areas of the world have observed up to 50% attrition to HIV care, with many of these patients not returning to care because of death [141]. Better understanding of attrition among HIV-infected patients in care is essential to evaluating HIV clinical care provision and informing interventions for improving retention in care [142]. Retention in care could help improve individual clinical outcomes [143] and reduce risk of further HIV transmission in the community [144].

There were an estimated 740,000 HIV-infected patients living in China as of 2009 [145]. The major routes of HIV transmission in China include injection drug use (IDU), blood transfusion/former plasma donation, and heterosexual contact [146]. China initiated free cART provision through the National Free Antiretroviral Treatment Program (NFATP) in 2002. As of the end of 2009, over 80,000 HIV-infected patients had received cART through NFATP [53]. The effectiveness of this program in reducing mortality has been described previously [147, 148]. However, little is known about retention in HIV care among HIV-infected patients in China. The purpose of this study was to describe temporal trends in attrition and identify factors associated with greater risk of attrition among patients receiving cART through the Chinese NFATP Program from 2003 to 2010.

Methods

Study population

The study population included all HIV-infected patients receiving cART through the Chinese NFATP from 1 January 2003 to 31 December 2010. The NFATP is managed by the Division of Treatment and Care in the National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention. Detailed descriptions relevant to the management, process and methods of the Chinese NFATP have been published [134, 149]. The program used standardized paper based case report forms which were completed by local health workers and then faxed to a central office in the Division of Treatment and Care [135]. In 2010, a web-enabled electronic data collection system was implemented. At the visit when patients start cART, a standardized form for initial patient assessment is completed and baseline information is collected, including demographic data,

suspected HIV infection exposure route, clinical symptoms and signs, and laboratory test results. Subsequent follow up visits are scheduled for 2, 4, 8 and 12 weeks following cART initiation, and then every 3 months thereafter.

From its inception, NFATP provided free cART to all HIV-infected patients with a CD4 cell counts below 200 cells/ μL, a total lymphocyte counts <1200 cells/ μL or a World Health Organization (WHO) stage III or IV. At the beginning of 2008, patients with CD4 cell counts <350 cells/ μL became eligible for free cART in accordance with updated WHO guidelines [135].

For these analyses we included all HIV-infected adults who were ART-naïve at the time they initiated free cART through NFATP. Henan Province did not submit data to NFATP until July 1, 2006; therefore, patients residing in Henan Province who initiated cART before that date were excluded from this analysis (n=16,609) [150]. Additionally we excluded patients who did not have any recorded follow-up (n=2,896), consistent with prior work in this area [151], and those who initiated cART less than 210 days (approximately seven months) prior to 31 December 2010 to allow for adequate follow-up (n=14,195).

This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Measurements

Attrition was defined as not having a visit for at least 210 days. This is approximately seven months, which allows leniency for those who miss a standard three-month NFATP visit but are seen within four weeks of the following scheduled NFATP visit. Moreover, this seven month definition is roughly similar to the definition of six months used in prior studies [46, 138]. In sensitivity analyses, we assessed the effect of using different time intervals to

define attrition, including 180, 270 and 360 days from last observation. Factors measured at baseline included age, gender, marital status, suspected HIV exposure route, initial cART regimen, CD4 cell counts, alanine aminotransferase and hemoglobin at cART initiation. Baseline symptoms recorded include fever, cough, sputum production, dyspnea, chest pain, night sweat, diarrhea, nausea, projectile vomiting, headache, declining vision, blurred vision, rash, thrush, oral hairy leukoplakia, and lymphadenopathy. For these analyses, we summed the number of symptoms reported for each patient as a measure of clinical symptom severity. Antiretroviral therapy regimens were categorized as: neviripine (NVP) with lamivudine (3TC) and either zidovudine (AZT) or stavudine (D4T); efavirenz (EFV) with 3TC and either AZT or D4T; NVP and didanosine (DDI) and either AZT or D4T; and all other regimens. Health care setting (general hospital, infectious diseases hospital, centers for diseases control clinic, health care center at township level, village clinic and prison hospital), area of residence (eastern, central and western region) and calendar year of cART initiation were also included.

Statistical analysis

Person-time was calculated as time from cART initiation to the first of attrition or date of censoring. Patients were censored at the date of death or 31 December 2010, whichever occurred first. The complement of the Kaplan-Meier survival curve was used to plot the cumulative incidence of attrition by levels of factors of interest. The log-rank test statistic was used to assess differences in survival curves.

Cox proportional hazard models were used to estimate unadjusted and adjusted hazard ratios and 95% confidence intervals (CI), and we assessed for deviations from the proportional hazard assumption. Based on the bivariable results, we identified factors

predictive of the outcome with a P value<0.2. These factors were jointly entered into a model. Then backward elimination was used to sequentially to remove covariates with the highest P-values such that the final model included only factors predictive of the outcome defined as a P value<0.05.

Given the relationship between type of antiretroviral therapy available through NFATP and calendar year of starting cART, we explored the relationship between type of therapy and attrition in models stratified by calendar year of cART initiation. As a sensitivity analysis we administratively censored follow-up time at 12 and 24 months following cART initiation rather than at 31 December 2010. Data were analyzed using SAS version 9.2 (SAS Institute, Cary NC, USA). All hypothesis testing was 2-sided, with α level of 0.05.

Results

Between 1 January 2003 and 31 May 2010, 67,732 HIV-infected patients who initiated cART through the Chinese NFATP were included in this analysis. Over one-third (37%) of patients were women, 51% were infected through heterosexual contact, 23% through blood transfusion/ former plasma donation, and 22% through IDU (Table 4.1). At cART initiation, the median age was 38 years (interquartile range [IQR]: 32 - 45), and the median CD4 cell counts was 131 cells/ μL (IQR: 42 - 220). The median year of cART initiation was 2008 (IQR: 2007 - 2009). The initial cART regimen prescribed was predominantly NVP and 3TC with either AZT or D4T (70%).

Patients contributed a median of 20 months of follow-up (IQR: 11 - 34) and 8 visits (IQR: 5 - 13). The overall person-time contributed was 137,792 person-years. Of the 67,732 HIV-infected patients, 9,969 were lost to HIV care, and the remaining 57,763 were

administratively censored (7,390 of these 57,763 were censored at death). Among those administratively censored the median time on study was 22 months (IQR: 13 - 37), and among those who died the median time to death was 4 months (IQR: 1 - 11). The cumulative probability of attrition from cART initiation was 9% at 12 months, 13% at 18 months, 16% at 24 months and 24% at 60 months (Figure 4.1).

A number of factors were associated with attrition in unadjusted analyses, including younger age, male gender and being single or divorced (Table 4.2). Patients infected through IDU were more than twice as likely to be lost to HIV care [crude Hazard Ratio (cHR) 2.20, 95% CI: 2.10, 2.30] as those infected by heterosexual contact (Figure 4.2). Patients initiating cART in the central region of China were less likely to be lost to HIV care than patients living in other areas of China, and patients who received HIV care at larger and more centralized health care settings were more likely to be lost to care than patients receiving care at village level clinics. In multivariable analyses the direction of these relationships persisted although some were notably attenuated, particularly the association between attrition and type of health care setting.

Patients with higher CD4 cell counts at cART initiation were more likely to be lost to care (Figure 4.3). The hazard of attrition among patients with CD4 cell counts greater than 350 cells/ μL was 1.6 times greater than for patients with CD4 cell counts less than 50 cells/ μL (cHR=1.57; 95% CI:1.41, 1.74). The hazard of attrition was relatively similar among patients with CD4 cell counts less than 350 cells/mL at cART initiation. The relationship between CD4 cell count and attrition persisted after multivariable adjustment (Table 4.2). Patients with lower hemoglobin (cHR=1.24; 95% CI: 1.12, 1.37) and higher ALT (cHR=1.28; 95% CI: 1.16, 1.41) were also more likely to be lost, although ALT did not

remain predictive in multivariable analyses. Patients with more than four symptoms at cART initiation had a higher hazard of attrition, even after accounting for other characteristics.

Notably, attrition decreased with increasing cART initiation calendar year (Figures 4.4) and among patients who initiated modern cART regimens (including 3TC with either NVP or EFV) (Figures 4.5). These relationships were consistent in multivariable adjusted analyses (Table 4.2). To further assess the relationship between calendar year of cART initiation and type of regimen received, we compared cART regimens containing and not containing lamivudine: We observed a persistent effect of lamivudine associated with less attrition in models adjusting for cART initiation calendar year and those stratified by cART initiation calendar year (Table 4.3).

We assessed the effect of cART initiation calendar year with varying lengths of follow-up: We fit models to data where we administratively censored follow-up at 12 and at 24 months (Table 4.4). The reductions in attrition in more recent calendar years persisted in all models and were comparable to results observed relying on all patient observation time available. In additional sensitivity analyses, using different time intervals to define attrition, including 180, 270 and 360 days from last observation, our results were consistent irrespective of the definition of attrition we employed (data not shown). Finally we evaluated the effect of excluding patients who were only seen once by NFATP at their initial patient visit (n=2,896). Our results were unaltered when we included this group of patients in our main analyses (data not shown).

Discussion

At one year following cART initiation the cumulative probability of attrition was 9% and rose to 24% at 5 years among patients receiving free antiretroviral therapy in China

between 2003 and 2010 through the NFATP. This degree of retention in care is slightly better than that observed in low-income areas of the world (approximately 15% at one year) and slightly worse than that observed in high-income areas of the world (approximately 5% at one year) [18]. In a recent study conducted in Uganda attrition rates of 16%, 30% and 39% were observed at 1, 2 and 3 years following cART initiation, respectively [138].

Attrition was associated with both individual and contextual factors. Consistent with prior studies patients who acquired HIV through IDU were at substantial risk of being lost to care. In this study 22% of patients accessing HIV care were IDU, in comparison to 39% of HIV infections reported nationally [146]. This observation highlights that IDU encounter problems with both initiating and remaining in HIV care. In contrast to previous studies where either CD4 cell counts did not affect attrition or patients with lower CD4 cell counts had poorer retention [26, 37], among Chinese patients in NFATP we observed greater attrition among patients with higher CD4 cell counts. This result suggests that unrecognized mortality may not be a substantial underlying cause of attrition in this study population. However, attrition was higher among patients with lower hemoglobin, which has been associated with greater mortality [100, 151].

We observed encouraging results that in more recent calendar years and with the provision of newer cART regimens patients were retained in care longer. In multivariable analyses we did not observe substantial differences in attrition by type of clinic. Other studies conducted in low-income settings have found a similar attrition equality across large and small health care settings [123, 124, 152].

Our study is one of the largest to evaluate retention in HIV care and the only study to date to be carried out in China. However there are limitations to the present study. We were

not able to link the study population with death registries, nor was there active follow-up of patients lost to care. Therefore, our estimate of attrition includes patients who died but their death was not reported to the clinic where they were receiving HIV care. In prior studies conducted primarily in Africa as many as one-half of patients not returning to HIV care were found to be deceased when active tracing was available [24, 45, 49]. We do not know the outcomes of patients lost to follow-up in NFATP; however, given the relatively high CD4 cell counts among patients lost to care it is possibly that mortality may not have been a primary cause of attrition from HIV care in this population. We were also unable to evaluate the effect of longitudinal CD4 cell counts or HIV RNA levels on retention as these data were not available in the early years of the NFATP program. As additional information on these biomarkers becomes available it will be important to evaluate how they are associated with retention in HIV care. Additionally, given the unique nature of the Chinese NFATP program our results may not generalize to clinics in other areas of the world. For example, as part of NFATP all patients received free antiretroviral therapy as well as other needed HIV care. In other settings it has been shown that retention increases in programs that offer free ART [40]. Finally, we were not able to take into account hepatitis B (HBV) co-infection among HIV patients in this study. Although we were able to assess the effect of ALT on retention this marker alone may not have captured the entire effect of HBV co-infection, particularly given the high prevalence of HBV in China [153] and its relationship to greater mortality among HIV-infected patients [154].

These results have important implications for the management of HIV in China. Treatment of HIV, even at higher CD4 cell counts, clearly reduces transmission [144], and earlier treatment of HIV has measurable improvement on patient outcomes [104]. But these

benefits can only be achieved if HIV infection is detected, patients are efficiently referred for care, and following cART initiation patients remain in active clinical follow-up. Any substantial attrition, and certainly the level of attrition documented in this study, can erode the benefits of antiviral therapy and give rise to increased transmission of HIV and HIV drug resistance. Reassuringly to date prevalence of transmitted HIV drug resistance remains relatively low in China [155]. Our results identify patients most likely to be lost, and several factors that help to explain loss. These results must be used to design programs to keep HIV-infected people in care, and over a very long period of time.

Table 4.1 Characteristics of 67,732 HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010

Characteristic	N (%) or Median (IQR)
Age (years)	
Median (IQR)	38 (32 - 45)
18-29	11509 (17%)
30-44	38200 (56%)
≥45	18023 (27%)
Gender	
Female	24930 (37%)
Male	42798 (63%)
Marital status	
Single	10875 (16%)
Married	46434 (69%)
Divorced	4864 (7%)
Widowed	5399 (8%)
HIV exposure	
Blood transfusion/former plasma donation	14555 (23%)
Intravenous drug use	13735 (22%)
Homosexual transmission	2826 (4%)
Heterosexual transmission	32194 (51%)
Area of residence	
Eastern region	8359 (12%)
Central region	21278 (32%)
Western region	38095 (56%)
Health care setting	
General hospital	26801 (40%)
Infectious diseases hospital	12321 (18%)
Centers for diseases control clinic	16019 (24%)
Health care center at township level	9496 (14%)
Village clinic	2000 (3%)
Prison hospital	646 (1%)
CD4 counts (cells/ μL)	
Median (IQR)	131 (42 - 220)
0-49	17692 (28%)
50-199	26648 (42%)
200-349	17465 (27%)
≥350	1760 (3%)
Hemoglobin (g/L)	
Median (IQR)	124 (108 - 140)
0-79	2612 (4%)
≥80	59269 (96%)
ALT (U/L)	
Median (IQR)	28 (18 - 44)
≥100	2421 (4%)
0-99	58875 (96%)

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Table 4.1 Characteristics of 67,732 HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (continued)

Characteristic	N (%) or Median (IQR)
Number of baseline symptoms	
≥4	18308 (27%)
2-3	15257 (22%)
1	9214 (14%)
0	24953 (37%)
Initiation cART regimen	
NVP+3TC+AZT	22179 (33%)
NVP+3TC+D4T	25336 (37%)
NVP+DDI+AZT	2557 (4%)
NVP+DDI+D4T	1970 (3%)
EFV+3TC+AZT	7052 (10%)
EFV+3TC+D4T	6440 (10%)
Other regimens	2198 (3%)
Year of cART initiation	
2003-2004	2182 (3%)
2005-2006	9880 (15%)
2007-2008	27149 (40%)
2009-2010	28521 (42%)

Note ALT=alanine aminotransferase; cART=Combination Antiretroviral Therapy; NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; D4T=stavudine; DDI=didanosine; EFV=efavirenz;

Table 4.2 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010

Characteristic	**Unadjusted HR (95% CI)**	***Adjusted HR (95% CI)**
Age (years)		
18-29	1.52 (1.43 -1.61)	1.10 (1.02 - 1.19)
30-44	1.28 (1.22 -1.34)	0.94 (0.88 - 1.00)
≥45	1	1
Gender		
Male	1.30 (1.24 - 1.35)	1.09 (1.03 - 1.15)
Female	1	1
Marital status		
Divorced	1.41 (1.31 - 1.51)	1.30 (1.20 - 1.41)
Single	1.62 (1.55 - 1.70)	1.26 (1.18 - 1.34)
Widowed	0.95 (0.88 - 1.03)	1.10 (1.01 - 1.21)
Married	1	1
HIV exposure		
Blood transfusion/former plasma donation	0.83 (0.78 - 0.88)	0.74 (0.67 - 0.82)
Intravenous drug use	2.20 (2.10 - 2.30)	1.87 (1.76 - 1.98)
Homosexual transmission	0.53 (0.45 - 0.62)	0.52 (0.43 - 0.61)
Heterosexual transmission	1	1
Area of residence		
Eastern region	0.92 (0.86 - 0.97)	1.04 (0.96 - 1.12)
Central region	0.61 (0.58 - 0.64)	0.67 (0.61 - 0.74)
Western region	1	1
Health care setting		
General hospital	2.60 (2.22 - 3.05)	1.19 (0.96 - 1.48)
Infectious diseases hospital	2.09 (1.77 - 2.46)	1.09 (0.87 - 1.36)
Centers for diseases control clinic	1.67 (1.42 - 1.96)	1.02 (0.82 - 1.27)
Health care center at township level	1.78 (1.50 - 2.10)	1.42 (1.15 - 1.76)
Prison hospital	5.99 (4.89 - 7.33)	2.33 (1.80 - 3.01)
Village clinic	1	1
CD4 counts (cells/ μL)		
≥350	1.57 (1.41 - 1.74)	1.76 (1.55 - 2.00)
200-349	1.12 (1.06 - 1.19)	1.07 (1.00 - 1.14)
50-199	1.01 (0.96 - 1.06)	0.99 (0.93 - 1.05)
0-49	1	1
Hemoglobin (g/L)		
0-79	1.24 (1.12 - 1.37)	1.24 (1.10 - 1.39)
≥80	1	1
ALT (U/L)		
≥100	1.28 (1.16 - 1.41)	
0-99	1	
Number of baseline symptom		
≥4	1.07 (1.02 - 1.13)	1.07 (1.01 - 1.14)
2-3	0.95 (0.90 - 1.00)	0.98 (0.92 - 1.04)
1	0.96 (0.90 - 1.02)	0.96 (0.89 - 1.04)
0	1	1

Table 4.2 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (continued)

Characteristic	**Unadjusted HR (95% CI)**	***Adjusted HR (95% CI)**
Initiation cART regimen		
NVP+3TC+AZT	0.90 (0.83 - 0.97)	0.95 (0.88 - 1.03)
NVP+3TC+D4T	0.92 (0.85 - 0.99)	0.86 (0.79 - 0.93)
NVP+DDI+AZT	1.19 (1.07 - 1.33)	1.58 (1.35 - 1.86)
NVP+DDI+D4T	1.18 (1.06 - 1.32)	0.92 (0.77 - 1.10)
EFV+3TC+AZT	1	1
EFV+3TC+D4T	0.89 (0.81 - 0.98)	0.83 (0.75 - 0.92)
Other regimens	1.32 (1.18 - 1.47)	1.29 (1.12 - 1.48)
Year of cART initiation		
2003-2004	2.24 (2.05 - 2.44)	3.29 (2.84 - 3.81)
2005-2006	1.71 (1.61 - 1.82)	1.70 (1.58 - 1.83)
2007-2008	1.31 (1.24 - 1.38)	1.25 (1.17 - 1.32)
2009-2010	1	1

*****Adjusted hazard ratios are based on one model including all characteristics listed in column except ALT. Note: HR = hazard ratio; 95% CI = 95% Confidence Interval; ALT=alanine aminotransferase; cART=Combination Antiretroviral Therapy; NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; D4T=stavudine; DDI=didanosine; EFV=efavirenz.

Table 4.3 Association between initial combination antiretroviral regimen (Lamivudine /Non-lamivudine) and time to attrition overall and stratified by calendar year of therapy initiation

	HR (95% CI)
Unadjusted	
Non-lamivudine	1.33 (1.25 - 1.41)
Lamivudine	1.00
Adjusted all factors but NOT calendar year†	
Non-lamivudine	1.81 (1.65 - 1.98)
Lamivudine	1.00
Adjusted all factors and calendar year ‡	
Non-lamivudine	1.39 (1.26 - 1.54)
Lamivudine	1.00
Adjusted stratified by calendar year of cART initiation*	
2003-2004	
Non-lamivudine	N/A**
Lamivudine	N/A**
2005-2006	
Non-lamivudine	1.44 (1.24 - 1.67)
Lamivudine	1.00
2007-2008	
Non-lamivudine	1.81 (1.55 - 2.11)
Lamivudine	1.00
2009-2010	
Non-lamivudine	1.41 (0.97- 2.07)
Lamivudine	1.00

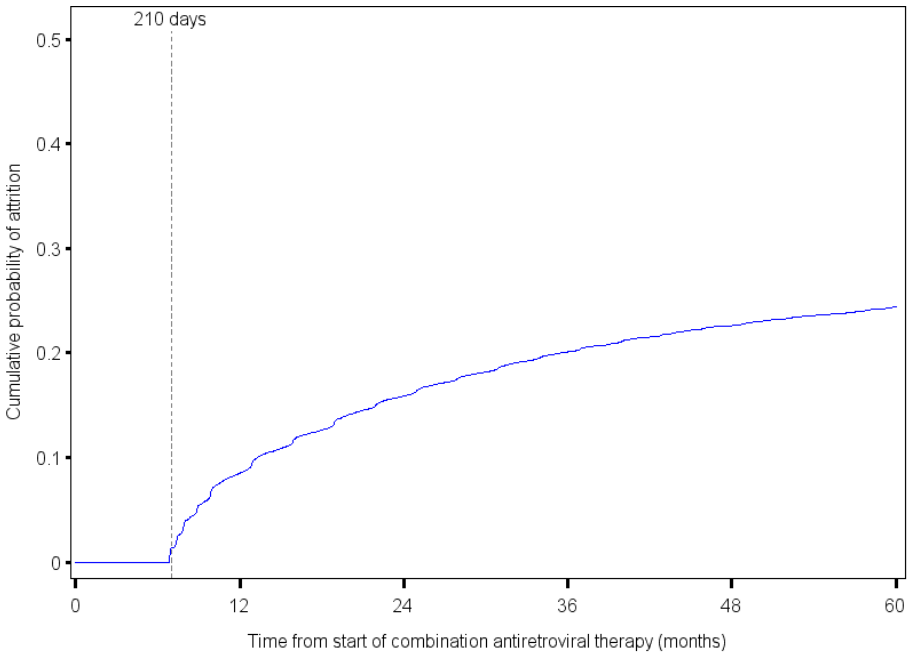
Note: HR=hazard ratio; 95% CI=95% Confidence Interval; †Includes initial regimen (lamivudine /Non-lamivudine) and patients' age, gender, marriage status, HIV exposure category, CD4 cell counts, hemoglobin level, clinical symptoms, area of residence, health care setting but excludes the year of starting therapy. ‡ Includes all factors plus the year of starting therapy. * Includes all factors but stratifies by the year of starting therapy. ** Because lamivudine was only available after 2005 in China; therefore we did not make estimates during 2003-2004.

Table 4.4 Association between the calendar year of combination antiretroviral therapy initiation and time to attrition stratified by observation time

	HR (95% CI)
Follow-up time truncated at 12 months of follow-up:	
Unadjusted	
2003-2004	2.18 (1.92 - 2.48)
2005-2006	1.81 (1.68 - 1.96)
2007-2008	1.30 (1.22 - 1.39)
2009-2010	1.00
Adjusted all factors but NOT initial regimens†	
2003-2004	4.28 (3.57 - 5.14)
2005-2006	1.77 (1.61 - 1.93)
2007-2008	1.20 (1.12 - 1.29)
2009-2010	1.00
Adjusted all factors and initial regimens‡	
2003-2004	4.08 (3.35 - 4.96)
2005-2006	1.85 (1.68 - 2.03)
2007-2008	1.23 (1.14 - 1.32)
2009-2010	1.00
Follow-up time truncated at 24 months of follow-up:	
Unadjusted	
2003-2004	2.23 (2.03 - 2.46)
2005-2006	1.74 (1.64 - 1.86)
2007-2008	1.29 (1.23 - 1.37)
2009-2010	1.00
Adjusted all factors but NOT initial regimens†	
2003-2004	3.58 (3.09 - 4.16)
2005-2006	1.72 (1.60 - 1.85)
2007-2008	1.22 (1.15 - 1.30)
2009-2010	1.00
Adjusted all factors and initial regimens‡	
2003-2004	3.14 (2.67 - 3.69)
2005-2006	1.77 (1.64 - 1.91)
2007-2008	1.25 (1.17 - 1.32)
2009-2010	1.00

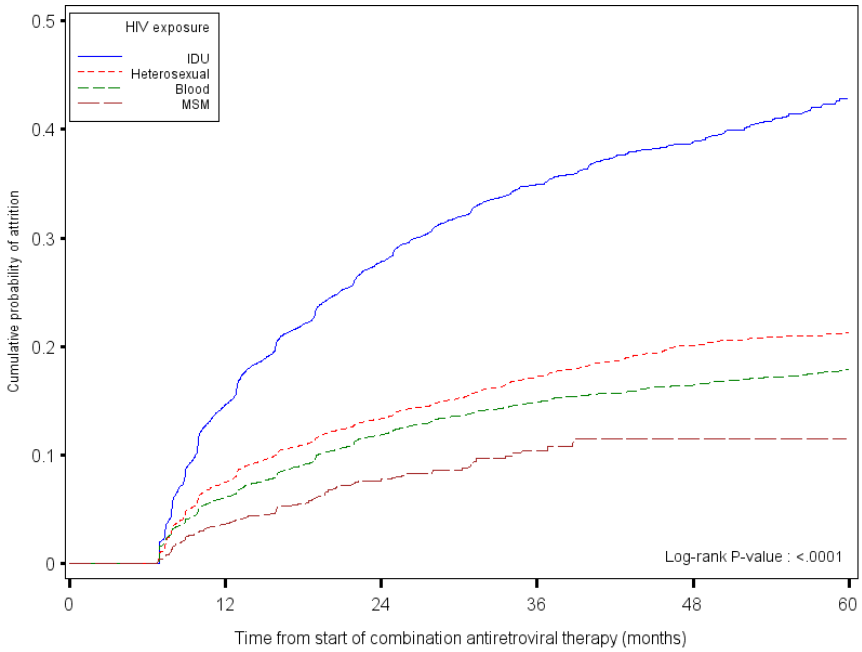
Note: HR=hazard ratio; 95% CI=95% Confidence Interval; † Includes the year of starting cART and patients' age, gender, marriage status, HIV exposure category, CD4 cell counts at enrollment, hemoglobin level, counts of baseline symptoms, area of residence, health care setting and initial regimens but excludes initial regimens. ‡ Includes all factors plus initial regimens.

Figure 4.1 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003 - 2010



No. at risk	67732	49064	28442	15403	7247	3006

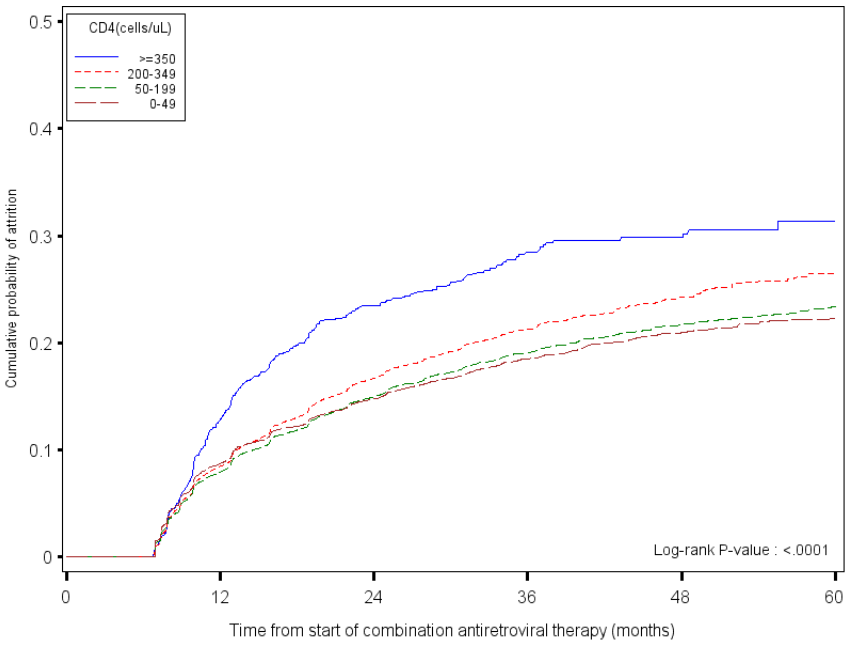
Figure 4.2 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by HIV exposure group



No. at risk						
IDU	13735	9447	5185	2490	1039	315
Heterosexual	32194	23061	12545	6189	2581	858
Blood	14555	11415	8011	5306	2982	1599
MSM	2826	1992	776	297	121	45

Note: blood = blood transfusion/former plasma donation; IDU = injection drug use; MSM= men who have sex with men.

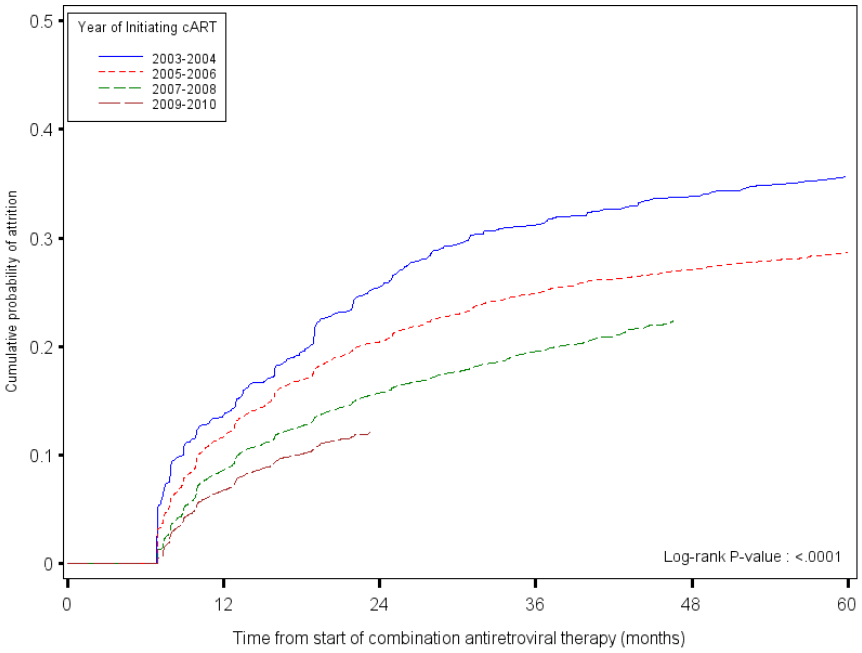
Figure 4.3 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by CD4 counts



No. at risk

≥350	1760	1308	771	409	185	64
200-349	17465	12961	6524	2953	1131	449
50-199	26648	20058	11946	6555	3044	1136
0-49	17692	11953	7226	4052	1902	668

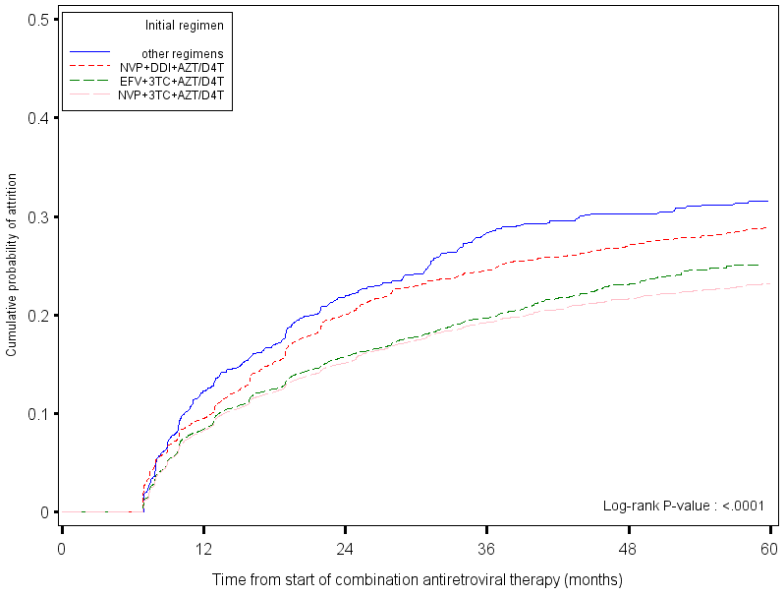
Figure 4.4 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by calendar year of therapy initiation



No. at risk

2003-2004	2182	1687	1424	1285	1202	1135
2005-2006	9880	7749	6819	6314	6023	1871
2007-2008	27149	22490	20199	7804	22	0
2009-2010	28521	17138	0			

Figure 4.5 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by type of initial regimen.



No. at risk						
Other regimens	2198	1448	941	634	495	392
NVP+DDI+AZT/D4T	4527	3526	2743	1994	1389	925
NVP+3TC+AZT/D4T	47515	34937	20060	10658	4484	1380
EFV+3TC+AZT/D4T	13492	9153	4698	2117	879	309

Note: NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; D4T=stavudine; DDI=didanosine; EFV=efavirenz

V. DECREASING EXCESS MORTALITY OF HIV-INFECTED PATIENTS INITIATING ANTIRETROVIRAL THERAPY: COMPARISON WITH MORTALITY IN GENERAL POPULATION IN CHINA, 2003-2009

Introduction

Combination antiretroviral therapy (cART) provision enables human immunodeficiency virus (HIV)-infected patients to suppress HIV replication [156-158], leading to substantially lower morbidity and mortality in both resource rich and poor areas of the world [17, 159]. A number of prior studies have observed notable reductions in mortality across calendar time with increasing uptake of more efficacious cART [75, 86, 160]. However, mortality among HIV-infected patients remains higher in resource poor areas even where cART is available [18].

Reductions in mortality from HIV-infection have also been narrowing the gap in life expectancy comparing HIV-infected patients to the general population [116, 119, 161, 162]. Among some HIV-infected patients life expectancy may approach that observed in the general population [117, 163]. For example, among West and South African patients participating in the International epidemiological Databases to Evaluate AIDS project who initiated cART at higher CD4 counts life expectancy estimates approach those of HIV-uninfected individuals [115]. Mortality and life expectancy contrasts comparing HIV-infected patients receiving cART to the general population assess the effectiveness of provided HIV therapy at a population level. These types of analyses also provide data for

policy makers for assessing future needs of HIV-infected patients and in planning allocation of health care and other resources.

The Joint United Nations Programme on HIV/AIDS estimated that as of 2009, 740,000 (range 540,000-1,000,000) adults and children were living with HIV in China [145]. Since 2002, HIV-infected patients in China have had access to free cART through the National Free Antiretroviral Treatment Program (NFATP) [137], and as of 2009 over 80,000 patients received cART through this program [53]. As elsewhere around the world, HIV-infected patients receiving cART experience notable reductions in morbidity and mortality in China [53, 148, 164]. Although NFATP only launched the national free cART program in the last decade, notable decreases in mortality across calendar time have already been reported [139]. However, this prior work has concentrated on internal comparisons of mortality among HIV-infected patients over time. In the present study we compare mortality estimates between HIV-infected patients receiving cART through NFATP with the general Chinese population from 2003 and 2009. We estimated both excess mortality and standardized mortality ratios over calendar time and evaluated risk factors for excess mortality.

Methods

Study population

Patients receiving free cART through NFATP between 1 January 2003 and 31 December 2009 were included [134, 137, 149]. Patients were cART eligible if they had a CD4 count below 200 cells/ μL (increased to 350 cells/ μL in 2008), a total lymphocyte counts <1200 cells/ μL or a World Health Organization stage III or IV clinical condition [135]. Standardized paper-based case report forms were completed by local health workers.

Information included demographic data, HIV exposure route, clinical symptoms and signs, cART administered and laboratory test results. Subsequent follow up visits occurred at 2, 4, 8 and 12 weeks following cART initiation, and then every 3 months thereafter. We excluded patients who did not have information on area of residence (n=10,669) and who did not have any follow-up visit information before 15 December 2009 (n=714). This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Measurements

Factors measured at the first visit included age, sex, HIV exposure route, initial cART regimen, CD4 cell count, type of health care setting and area of residence (rural vs. urban). Antiretroviral therapy regimens were categorized as: neviripine (NVP) with lamivudine (3TC) and either zidovudine (AZT) or stavudine (d4T); efavirenz (EFV) with 3TC and either AZT or D4T; NVP and didanosine (DDI) and either AZT or D4T; and all other regimens. HIV exposure route included infection through blood transfusion/ former plasma donation, sexual transmission and injection drug use (IDU). Information on death, including reason and date of death, was available through the NFATP treatment withdrawal forms. These forms were also completed by local health workers and sent to central NFATP offices by DataFax (Clinical DataFax Systems, Hamilton, Ontario, Canada). Forms were completed on all patients known to have died at the local level through passive surveillance. Mortality data for the general Chinese population was obtained from *China Health Statistic Year Book 2004* to *2010*. These national death statistics are based on a passive surveillance system, i.e. the Ministry of Health-vital registration system, to report death cases to a central national repository [165].

Statistical analysis

Person-time was calculated from the date when patients initiated cART to the date of death or date of censoring. Patients were censored either at the date of withdrawal from NFATP or 31 December 2009, whichever occurred first. The reason for withdrawal included loss to follow up, treatment interruption or transferring to another health care facility. Loss to follow-up was defined as missing more than 3 visits and we used the latest date seen in clinic as the date of withdrawal.

Observed mortality rates were calculated as number of deaths divided by person-year at risk and corresponding 95% confidence intervals (95% CIs) were calculated based on Poisson distribution [166]. Expected number of deaths was estimated by applying the probability of death in the general Chinese population to the study population in each calendar year. Patients were matched to the general population on age (by 5 year age group), sex, area of residence (urban versus rural) and calendar year.

Excess mortality rates were calculated as the difference between observed deaths in the study population and that expected based on estimates from the general population. Standardized mortality ratios (SMR) were calculated as the ratio of the observed number of deaths in the study population to that expected from estimates based on the general population. As measures of precision we calculated 95% CIs for both excess mortality rates and standardized mortality ratios [166]. Excess mortality rates and standardized mortality ratios were estimated within strata defined by calendar year interval (2003-2004, 2005-2007 and 2008-2009). This categorization was chosen to: minimize heterogeneity within groups; correspond with major therapeutic changes across calendar time; and preserve adequate sample sizes within strata. Further stratification of estimates was done according to patients'

age, sex, HIV exposure route, CD4 count at cART initiation, area of residence, type of health care settings and type of first cART regimen received.

We further evaluated changes in excess mortality across calendar time in multivariable Poisson regression models [111]. In this relative survival model, the observed number of deaths in each patient stratum was modeled with a Poisson process and we used the expected number of deaths in each stratum as an offset. Time was categorized into one year increments from cART initiation, assuming a piecewise constant hazard within each year after starting cART. Excess hazard ratios (eHRs) and associated 95% CIs were obtained as the antilog of the coefficient from this relative survival model. We examined changes in relative survival across calendar time adjusting for age, sex, HIV-exposure category, CD4 count, initial cART regimen, type of health care setting and area of residence. In this case the interpretation of eHR comparing calendar years is similar to other survival models, such that the index group of patients experiences an instantaneous risk of death "X" times the risk among patients in the reference group, accounting for expected background mortality and the other patient characteristics included in the model. In all analyses hypothesis testing was 2-sided and an alpha of 0.05 was used to indicate a statistically significant difference. All analyses were done using SAS version 9.2 (SAS Institute, Cary NC, USA).

Results

Overall 64,836 HIV-infected patients with known area of residence initiated cART in the Chinese NFATP between 2003 and 2009 and were included in this analysis. The proportion of patients receiving treatment scaled up over the years and almost half of patients initiated cART during 2008 and 2009 (47%) (Table 5.1). The median age at cART initiation

was 38 years [interquartile range (IQR): 33 - 46], 40% of patients were women, and 70% lived in rural areas. Across time patients appeared younger at cART initiation, were more likely to be men, and more likely to live in urban areas. In 2003 and 2004 nearly all patients were infected through blood transfusion/former plasma donation (95%), and this decreased to 18% by 2008 and 2009.

The median CD4 count at cART initiation decreased across time from 223 cells/mL in 2003/2004 to 141 cells/mL in 2008/2009. Although NVP remained the most common anchor agent provided across time, the use of 3TC replaced DDI in 2005/2006. Specifically in 2003/2004 patients predominantly received NVP and DDI with either AZT or D4T (89%), in comparison in 2008/2009 the most common first cART regimen was NVP and 3TC with either AZT or D4T (73%).

Patients were followed on average for a median of 1.5 years (IQR: 0.5 - 3.4), contributing a total of 135,509 person-years of follow-up (Table 5.2). Overall 13% of patients were known to have died (n=8,577), with an observed mortality rate of 6.3 deaths/100 person-years (95% CI: 6.2 - 6.4). The crude observed mortality rate decreased across calendar time from 9.5 to 5.6 deaths /100 person-years from 2003/2004 to 2008/2009.

The overall excess mortality rate was 6.0 deaths/100 person-years (95% CI: 5.9, 6.1). Excess mortality fell from 9.1 deaths/100 person-years (95% CI: 8.5, 9.8) in 2003/2004 to 5.2 deaths/100 person-years (95% CI: 5.0, 5.4) in 2008/2009 (Table 5.2). The reductions in excess mortality rates across calendar time were evident within all strata of patient characteristics, including age, sex, CD4 count at cART initiation and type of initial cART (Table 5.3). In unadjusted analyses excess mortality rates were higher among older patients in each stratum of calendar years, although younger patients in 2003/2004 also had high

excess mortality (Figure 5.1). After adjustment for other patient characteristics, including age, sex, HIV exposure route, CD4 count, number of baseline symptoms, initial cART regimen, area of residence, and health care setting, the adjusted excess mortality rates were higher in older patients across all calendar periods (Figure 5.3). The most dramatic reductions in unadjusted excess mortality rates across calendar time occurred among patients with low CD4 counts at cART initiation (Figure 5.2) and comparable results were obtained in the adjusted analyses (Figure 5.4).

The overall SMR was 20.1 (95% CI: 19.7, 20.5). The SMR decreased from 30.8 (95% CI: 28.6, 33.1) to 17.0 (95% CI: 16.5, 17.6) from 2003/2004 to 2008/2009 (Table 5.2). In general SMR results stratified by patient characteristic were comparable to results observed for excess mortality rates (Table 4, Figure 5.5). As observed with excess mortality rates, the reduction in SMR across calendar time was most dramatic among patients initiating cART at low CD4 counts. Among patients with CD4 counts below 50 cells/ μL the SMR declined from 103.6 (95% CI: 86.2, 124.5) to 32.2 (95% CI: 30.5, 34.0) from 2003/2004 to 2008/2009.

The adjusted excess mortality rate decreased from 2003/2004 to 2008/2009, with an eHR of 1.27 (95% CI: 1.11, 1.45), indicating the risk of death was nearly 30% higher in 2003/2004 than 2007/2008, adjusting for background mortality and other patient characteristics including age, sex, HIV exposure route, area of residence, health care setting, CD4 count, number of baseline symptoms, and initial cART regimen (Table 5.5). Patients who were older at cART initiation were at a greater risk of dying with an eHR of 1.63 (95% CI: 1.47, 1.82) comparing patients more than 45 years of age to those less than 30. Men, patients living in rural areas, and those exposed to HIV through IDU were also at higher risk

of death. Patients who received care at larger and centralized medical care facilities appeared to be at lower risk than those who received care at smaller local centers. Excess mortality decreased with increasing CD4 counts at cART initiation, with patients who started cART with CD4 counts less than 50 cells/ μL at almost 10 times the risk of death compared to patients with CD4 counts greater than 350 cells/ μL (eHR=9.92; 95% CI, 8.59 - 11.44).

Discussion

In this study including over 64,000 HIV-infected patients initiating cART in China, we found both observed and excess mortality rates decreased more than 30% from 2003 to 2009. Mortality ratios standardized to the general Chinese population also decreased by over 30% from 2003 to 2009. The decreases in excess mortality rates and SMRs across calendar time were relatively consistently observed within all patient demographic and clinical characteristics, and after adjusting for a number of factors including age, CD4 count and cART regimen at therapy initiation, excess mortality decreased by over 20% from 2003/2004 to 2008/2009. These findings are consistent with prior studies which have reported reductions in observed and expected mortality rates and SMRs across calendar time among patients initiating cART in both resource rich and poor areas of the world [100, 114, 115, 163, 167].

The observed mortality rate in this study population (6 deaths/100 person-years) was higher in comparison to results from resource wealthy areas of the world (1 death/100 person-years) [167], but lower than that observed in Sub-Saharan Africa (8 deaths/100 person-years) [115]. The overall excess mortality we observed was similar to estimates from Sub-Saharan Africa (6 vs. 7 deaths/100 person-years, respectively), as were the SMRs (20

and 19, respectively) [115], but higher than reported in Europe and North America (excess mortality rate = 2 deaths/100 person-years [114] and SMR= 3 [167])

Notwithstanding the substantial decreases in mortality rates across calendar time, HIV-infected patients in this study population consistently had greater excess mortality in comparison to the general Chinese population. However there were notable differences in excess mortality rates among groups of patients defined by demographic and clinical characteristics. Among some groups of patient's mortality was less than 10 times the general population whereas among other groups this rose to over 100 times. The greatest differences in mortality were observed within CD4 count and age strata. The lowest excess mortality rates were among patients initiating cART at CD4 counts greater than 350 cells/ μL. This group of patients had less than 10 times the mortality of the general population in all calendar years. In comparison the highest excess mortality rates were observed among patients initiating cART with CD4 counts less than 50 cells/ μL. This group of patients had over 30 times the mortality of the general population even in the most recent calendar years. In adjusted analyses patients starting cART with CD4 counts less than 50 cells/ μL had nearly a 10-fold higher excess mortality compared to patients initiating cART at CD4 counts greater than 350 cells/ μL. These findings have been consistently reported from all areas of the world [115, 161] and underscore recent recommendations that cART be initiated at higher CD4 counts to optimize overall survival [104] and that additional efforts are needed for earlier HIV diagnosis and treatment initiation among many HIV-infected patients [168].

Overall excess mortality rates increased with increasing age. In multivariable analyses adjusting for CD4 count and other patient characteristics patients at least 45 years of age had over 1.6 times excess mortality in comparison to patients less than 30 years of age.

Other independent factors associated with excess mortality in multivariable analyses included being a male, patients infected through IDU in comparison to sexual transmission, patients residing in rural versus urban areas, and patients receiving HIV care at local health care centers in comparison to larger centralized hospital settings. Prior studies have also reported older age, male sex, and IDU as risk factors for excess mortality [18, 100, 114].

It is possible that the HIV-infected patients in this study population were different from the general population in other characteristics that we were not able to account for (age, sex, area of residence and calendar year) [162]. In other words, HIV-infected patients in China may be at greater risk of death than the general population for reasons other than HIV, such as a higher prevalence of other comorbidities (e.g., Hepatitis B or C infection). Death ascertainment relied on reports to HIV care providers, rather than links with centralized death registries, therefore we may be underestimating the true mortality rates. We were also unable to account for duration of HIV-infection, or virologic or immunologic response to cART. Observed mortality rates, excess rates and standardized mortality ratios would likely be lower among patients with better response to cART.

In summary, among HIV-infected patients receiving cART through the Chinese NFATP we have observed substantial decreases in excess mortality in comparison to the general Chinese population from 2003 to 2009. Further reductions will likely be achieved as NFATP is able to provide more efficacious first and second line cART regimens. Our results indicate that further reductions in mortality will follow if patients are identified earlier after HIV-infection and are successfully linked with HIV care.

Table 5.1 Characteristics of 64,836 HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2009

Characteristic†	**2003-2004**	**2005-2007**	**2008-2009**	**Total**
Total	11,366 (18%)	22,755 (35%)	30,715 (47%)	64,836 (100%)
Age (years)				
Median	41 (36 - 48)	38 (32 - 45)	38 (32 - 45)	38 (33 - 46)
18-29	507 (5%)	3,191 (14%)	5,307 (17%)	9,005 (14%)
30-44	6,722 (59%)	13,548 (60%)	16,979 (55%)	37,249 (57%)
≥45	4,137 (36%)	6,016 (26%)	8,429 (28%)	18,582 (29%)
Sex *				
Men	5,620 (49%)	13,497 (59%)	19,578 (64%)	38,695 (60%)
Women	5,746 (51%)	9,255 (41%)	11,136 (36%)	26,137 (40%)
HIV exposure*				
Blood transfusion/former plasma donation	10,787 (95%)	10,133 (47%)	5,114 (18%)	26,034 (42%)
Intravenous drug use	51 (1%)	3,667 (17%)	6,130 (21%)	9,848 (16%)
Sexual transmission	470 (4%)	7,652 (36%)	17,578 (61%)	25,700 (42%)
Area of residence				
Urban	469 (4%)	6,746 (30%)	12,531 (41%)	19,746 (30%)
Rural	10,897 (96%)	16,009 (70%)	18,184 (59%)	45,090 (70%)
Health care setting*				
General hospital	189 (2%)	6,344 (28%)	13,360 (44%)	19,893 (31%)
Infectious diseases hospital	234 (2%)	2,915 (13%)	5,304 (18%)	8,453 (13%)
Centers for diseases control clinic	873 (8%)	4,211 (19%)	6,551 (21%)	11,635 (18%)
Health care township level/prison hospital	10,042 (88%)	9,169 (40%)	5,270 (17%)	24,481 (38%)
CD4 count (cells/ μL)*				
Median	223 (120 - 361)	132 (45 - 217)	141 (46 - 230)	147 (51 - 240)
0-49	869 (11%)	5,552 (27%)	7,753 (26%)	14,174 (24%)
50-199	2,466 (32%)	9,082 (44%)	12,107 (41%)	23,655 (41%)
200-349	2,320 (30%)	4,724 (23%)	8,993 (30%)	16,037 (28%)
≥350	2,086 (27%)	1,411 (7%)	816 (3%)	4,313 (7%)

Table 5.1 Characteristics of 64,836 HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2009 (continued)

Characteristic†	**2003-2004**	**2005-2007**	**2008-2009**	**Total**
Number of baseline symptom				
0	1,313 (12%)	5,211 (23%)	11,855 (39%)	18,379 (28%)
1	1,097 (10%)	2,772 (12%)	4,271 (14%)	8,140 (13%)
2-3	3,116 (27%)	5,859 (26%)	6,763 (22%)	15,738 (24%)
≥4	5,840 (51%)	8,913 (39%)	7,826 (25%)	22,579 (35%)
Initiation regimen‡				
NVP+3TC+AZT	292 (2%)	2,958 (13%)	12,699 (41%)	15,949 (25%)
NVP+3TC+D4T	389 (3%)	11,897 (52%)	9,723 (32%)	22,009 (34%)
NVP+DDI+AZT	8,326 (73%)	4,027 (18%)	807 (3%)	13,160 (20%)
NVP+DDI+D4T	1,799 (16%)	916 (4%)	234 (1%)	2,949 (5%)
EFV+3TC+AZT	75 (1%)	897 (4%)	3,665 (12%)	4,637 (7%)
EFV+3TC+D4T	72 (1%)	1,534 (7%)	2,952 (9%)	4,558 (7%)
Other regimens	413 (4%)	526 (2%)	635 (2%)	1,574 (2%)

†Data are median (IQR) or number (%) unless otherwise stated;

* Missing values: Sex (n=4), HIV exposure (n=3,254), Health care setting (n=374), CD4 cell count (n=6,657)

‡ NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; d4T=stavudine; DDI=didanosine; EFV=efavirenz.

Table 5.2 Observed and excess mortality rates, and standardized mortality ratios, among 64,836 HIV-infected patients initiating combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program from 2003 - 2009

Mortality	2003-2004	2005-2007	2008-2009	Total
Observed death	733	3,815	4,029	8,577
Expected death	23.8	166.4	236.6	426.8
Person year at follow up	7,754	55,336	72,419	135,509
Observed mortality rate (95% CI)† (per 100 person-years)	9.5 (8.8 - 10.2)	6.9 (6.7 - 7.1)	5.6 (5.4 - 5.8)	6.3 (6.2 - 6.4)
Excess mortality rate (95% CI)‡ (per 100 person-years)	9.1 (8.5 - 9.8)	6.6 (6.4 - 6.8)	5.2 (5.0 - 5.4)	6.0 (5.9 - 6.1)
Standardized mortality ratio (95% CI)*	30.8 (28.6 - 33.1)	22.9 (22.2 - 23.7)	17.0 (16.5 - 17.6)	20.1 (19.7 - 20.5)

† Calculated as 100 × (observed death/person years at follow up)

‡ Calculated as 100× [(observed death-expected death)/person years at follow up)]

* Calculated as 100 × (observed death/ expected death)

Table 5.3 Excess mortality rates among 64,836 HIV-infected patients initiating combination antiretroviral therapy stratified by patient characteristics, the China National Free Antiretroviral Treatment Program 2003 - 2009†

Characteristic	**2003-2004**	**2005-2007**	**2008-2009**
Age			
18-29	11.0 (8.0 - 15.1)	5.9 (5.2 - 6.7)	3.3 (3.0 - 3.7)
30-44	9.2 (8.4 - 10.1)	6.1 (5.8 - 6.4)	5.1 (4.9 - 5.3)
≥45	8.8 (7.8 - 10.0)	7.7 (7.3 - 8.1)	6.5 (6.2 - 6.9)
Gender			
Men	11.3 (10.3 - 12.4)	7.9 (7.6 - 8.2)	6.1 (5.9 - 6.3)
Women	7.2 (6.4 - 8.1)	5.2 (4.9 - 5.5)	4.1 (3.9 - 4.3)
HIV exposure			
Blood transfusion/former plasma donation	9.1 (8.4 - 9.8)	6.7 (6.5 - 7.0)	5.5 (5.3 - 5.8)
Intravenous drug use	N/A‡	6.0 (5.2 - 6.9)	7.3 (6.8 - 7.9)
Sexual transmission	8.6 (5.3 - 13.8)	6.4 (5.9 - 7.0)	4.0 (3.8 - 4.3)
Area of residence			
Rural	9.1 (8.4 - 9.8)	6.6 (6.4 - 6.8)	5.6 (5.4 - 5.8)
Urban	10.9 (7.1 - 16.7)	6.4 (5.9 - 7.0)	4.3 (4.0 - 4.6)
Health care setting			
General hospital	19.1 (11.5 - 31.7)	6.5 (5.9 - 7.2)	5.2 (4.9 - 5.5)
Infectious diseases hospital	5.0 (2.4 - 10.5)	4.6 (4.0 - 5.4)	2.4 (2.1 - 2.7)
Centers for diseases control clinic	13.5 (10.7 - 17.1)	7.4 (6.8 - 8.1)	6.1 (5.7 - 6.5)
Health care under township level/prison hospital	8.8 (8.1 - 9.5)	6.6 (6.3 - 6.9)	5.7 (5.4 - 6.0)
CD4 count (cells/ μL)			
0-49	27.8 (23.1 - 33.4)	15.5 (14.6 - 16.4)	9.1 (8.6 - 9.6)
50-199	7.8 (6.4 - 9.4)	5.9 (5.5 - 6.3)	4.9 (4.6 - 5.2)
200-349	1.2 (0.7 - 1.9)	2.5 (2.2 - 2.8)	2.7 (2.5 - 3.0)
≥350	1.9 (1.3 - 2.8)	1.4 (1.2 - 1.7)	2.1 (1.8 - 2.5)
Number of baseline symptom			
0	8.0 (6.3 - 10.1)	2.9 (2.6 - 3.3)	2.6 (2.4 - 2.8)
1	5.6 (4.2 - 7.5)	4.8 (4.3 - 5.4)	4.5 (4.1 - 5.0)
2-3	6.3 (5.4 - 7.4)	6.4 (6.0 - 6.8)	5.6 (5.3 - 6.0)
≥4	12.1 (11.0 - 13.3)	8.5 (8.1 - 8.9)	7.1 (6.8 - 7.4)

Table 5.3 Excess mortality rates among 64,836 HIV-infected patients initiating combination antiretroviral therapy stratified by patient characteristics, the China National Free Antiretroviral Treatment Program 2003 - 2009† (continued)

Characteristic	**2003-2004**	**2005-2007**	**2008-2009**
Initiation regimen*			
NVP+3TC+AZT	5.2 (2.3 - 11.6)	5.7 (5.0 - 6.5)	4.7 (4.4 - 5.1)
NVP+3TC+D4T	0.8 (0.2 - 3.2)	7.6 (7.2 - 8.1)	4.9 (4.6 - 5.2)
NVP+DDI+AZT	10.8 (10.0 - 11.7)	6.8 (6.5 - 7.1)	6.0 (5.6 - 6.4)
NVP+DDI+D4T	6.5 (5.4 - 7.9)	4.8 (4.3 - 5.4)	4.0 (3.4 - 4.7)
EFV+3TC+AZT	N/A‡	2.9 (2.1 - 4.1)	4.8 (4.2 - 5.5)
EFV+3TC+D4T	N/A‡	7.5 (6.2 - 9.0)	6.7 (6.0 - 7.5)
Other regimens	4.8 (3.0 - 7.6)	4.8 (3.9 - 5.9)	7.1 (6.0 - 8.5)

†. All of excess mortality rates were per 100 person-years

‡N/A: excess mortality rates were not estimated within strata with fewer than 100 patients.

* NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; d4T=stavudine; DDI=didanosine; EFV=efavirenz.

Table 5.4 Standardized mortality ratios among 64,836 HIV-infected patients initiating combination antiretroviral therapy stratified by patient characteristics, the China National Free Antiretroviral Treatment Program 2003 – 2009

Characteristic	**2003-2004**	**2005-2007**	**2008-2009**
Age			
18-29	N/A*	114.9 (102.0 - 129.5)	70.8 (63.5 - 79.0)
30-44	54.1 (49.2 - 59.4)	37.8 (36.2 - 39.4)	31.6 (30.4 - 33.0)
≥45	16.8 (14.9 - 18.9)	13.4 (12.7 - 14.1)	9.1 (8.6 - 9.6)
Gender			
Men	30.9 (28.1 - 33.9)	21.9 (21.0 - 22.8)	15.6 (15.0 - 16.2)
Women	30.7 (27.4 - 34.3)	24.9 (23.7 - 26.2)	20.7 (19.6 - 21.8)
HIV exposure			
Blood transfusion/former plasma donation	30.7 (28.6 - 33.1)	22.5 (21.7 - 23.3)	16.2 (15.5 - 16.9)
Intravenous drug use	N/A*	47.6 (41.5 - 54.5)	53.9 (50.1 - 57.9)
Sexual transmission	28.2 (17.8 - 44.7)	22.6 (20.8 - 24.5)	13.3 (12.5 - 14.1)
Area of residence			
Rural	30.6 (28.5 - 33.0)	22.5 (21.7 - 23.3)	16.9 (16.3 - 17.5)
Urban	37.1 (24.4 - 56.3)	26.4 (24.2 - 28.7)	17.4 (16.4 - 18.6)
Health care setting			
General hospital	N/A*	29.0 (26.3 - 31.9)	19.8 (18.5 - 20.9)
Infectious diseases hospital	N/A*	16.4 (14.1 - 19.1)	9.0 (7.9 - 10.2)
Centers for diseases control clinic	56.7 (44.9 - 71.7)	28.8 (26.4 - 31.4)	20.9 (19.5 - 22.4)
Health care under township level/prison hospital	29.3 (27.1 - 31.7)	21.9 (21.1 - 22.7)	16.3 (15.6 - 17.1)
CD4 cell count (cells/ μL)			
0-49	103.6 (86.2 - 124.5)	61.3 (57.8 - 64.9)	32.2 (30.5 - 34.0)
50-199	25.0 (20.8 - 30.2)	20.0 (18.8 - 21.2)	15.4 (14.6 - 16.3)
200-349	4.8 (3.1 - 7.2)	9.4 (8.5 - 10.4)	9.7 (8.8 - 10.5)
≥350	7.1 (5.0 - 10.2)	5.6 (4.8 - 6.6)	6.7 (5.7 - 7.9)
Number of baseline symptom			
0	32.0 (25.5 - 40.2)	11.9 (10.6 - 13.4)	10.2 (9.4 - 11.1)
1	20.6 (15.5 - 27.3)	17.8 (15.9 - 19.9)	15.1 (13.8 - 16.6)
2-3	21.0 (18.0 - 24.6)	21.8 (20.5 - 23.2)	17.1 (16.1 - 18.2)
≥4	38.8 (35.4 - 42.6)	28.0 (26.8 - 29.2)	21.5 (20.6 - 22.5)

Table 5.4 Standardized mortality ratios among 64,836 HIV-infected patients initiating combination antiretroviral therapy stratified by patient characteristics, the China National Free Antiretroviral Treatment Program 2003 – 2009 (continued)

Characteristic	**2003-2004**	**2005-2007**	**2008-2009**
Initiation regimen†			
NVP+3TC+AZT	N/A*	24.8 (21.7 - 28.3)	17.4 (16.2 - 18.8)
NVP+3TC+D4T	3.4 (1.1 - 10.5)	28.3 (26.7 - 30.0)	16.5 (15.7 - 17.4)
NVP+DDI+AZT	35.7 (32.9 - 38.7)	22.1 (21.2 - 23.2)	16.4 (15.5 - 17.4)
NVP+DDI+D4T	22.7 (18.7 - 27.4)	16.6 (14.9 - 18.6)	12.1 (10.5 - 14.0)
EFV+3TC+AZT	N/A*	12.2 (8.8 - 16.9)	20.5 (17.9 - 23.5)
EFV+3TC+D4T	N/A*	25.6 (21.4 - 30.6)	21.5 (19.3 - 23.9)
Other regimens	18.9 (12.1 - 29.6)	19.0 (15.4 - 23.3)	23.8 (20.1 - 28.3)

* N/A: Standardized mortality ratios were not estimated within strata with expected deaths fewer than 0.5 patients.

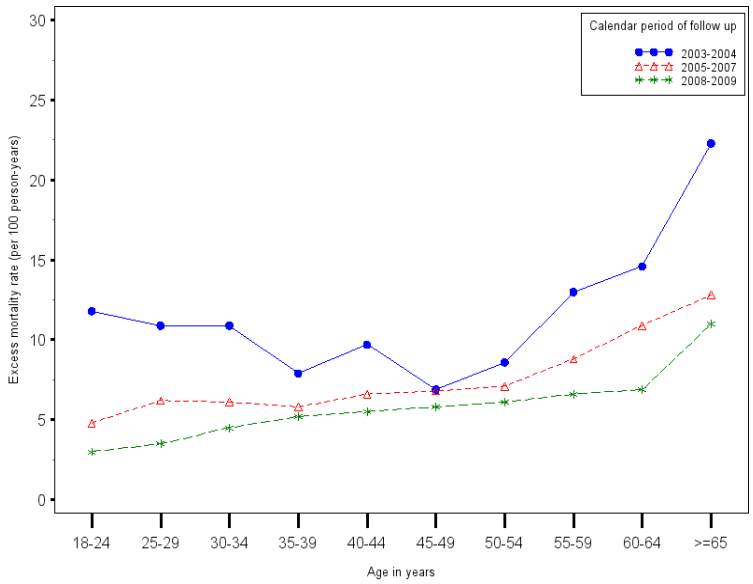
† NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; d4T=stavudine; DDI=didanosine; EFV=efavirenz.

Table 5.5 Adjusted excess hazard ratios among 64,836 HIV-infected patients initiating combination antiretroviral therapy, the China National Free Antiretroviral Treatment Program 2003 – 2009†

	eHR (95% CI)
Calendar period of follow up	
2003-2004	1.27 (1.11 - 1.45)
2005-2007	1.16 (1.09 - 1.23)
2008-2009	1.00
Age (years)	
≥45	1.63 (1.47 - 1.82)
30-44	1.27 (1.15 - 1.40)
18-29	1.00
Gender	
Men	1.37 (1.29 - 1.45)
Women	1.00
HIV exposure	
Blood transfusion/former plasma donation	0.98 (0.89 - 1.08)
Intravenous drug use	1.72 (1.57 - 1.88)
Sexual transmission	1.00
Area of residence	
Rural	1.17 (1.08 - 1.26)
Urban	1.00
Health care setting	
General hospital	0.85 (0.76 - 0.95)
Infectious diseases hospital	0.34 (0.30 - 0.40)
Centers for diseases control clinic	0.89 (0.81 - 0.97)
Health care under township level/prison hospital	1.00
CD4 count (cells/ μL)	
0-49	9.92 (8.59 - 11.44)
50-199	4.08 (3.55 - 4.70)
200-349	1.82 (1.56 - 2.11)
≥350	1.00
Number of baseline symptom	
≥4	2.10 (1.91 - 2.31)
2-3	1.65 (1.49 - 1.82)
1	1.35 (1.19 - 1.52)
0	1.00
Initiation regimen‡	
NVP+3TC+AZT	1.11 (0.94 - 1.31)
NVP+3TC+D4T	1.09 (0.93 - 1.27)
NVP+DDI+AZT	1.37 (1.17 - 1.62)
NVP+DDI+D4T	0.97 (0.80 - 1.17)
Other regimens	1.24 (1.00 - 1.54)
EFV+3TC+D4T	1.20 (1.00 - 1.43)
EFV+3TC+AZT	1.00

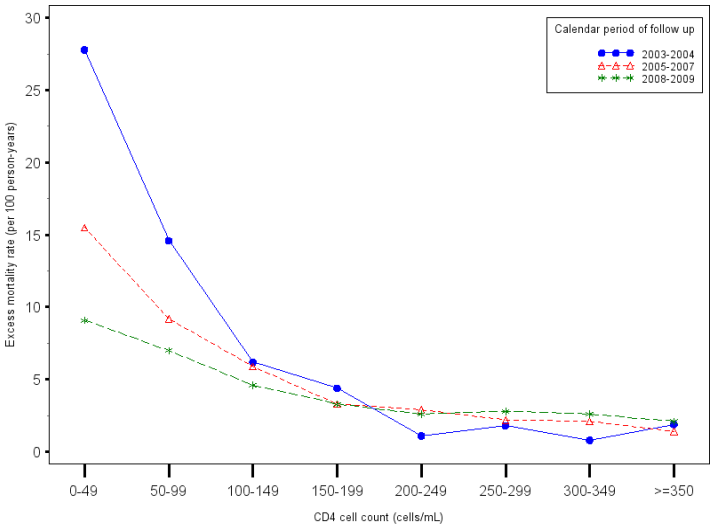
†Estimates from one model including all characteristics listed in table
‡ NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; d4T=stavudine; DDI=didanosine; EFV=efavirenz.

Figure 5.1 Excess mortality rates by calendar year interval among 64,836 HIV-infected patients initiating combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program 2003 – 2009 by age at therapy initiation.



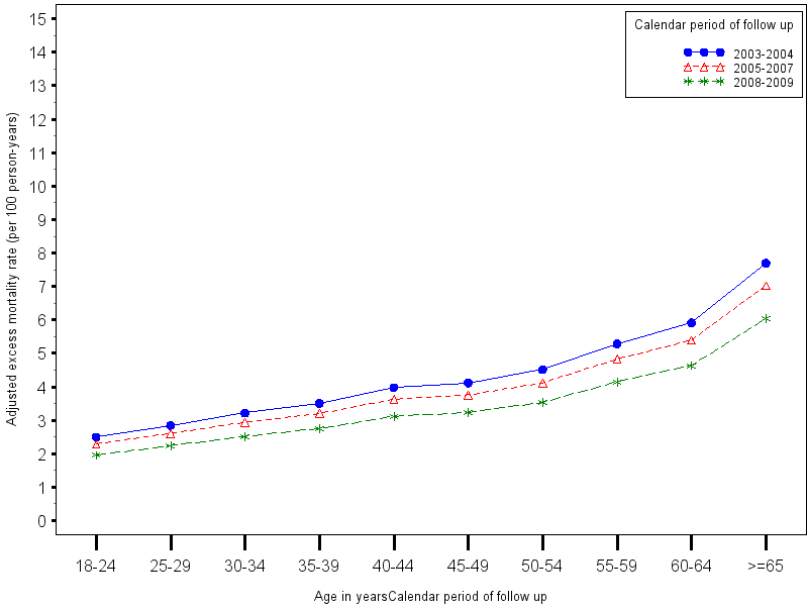
No.										
2003/2004	76	582	2156	3483	2950	2325	1943	726	238	95
2005/2007	1361	5110	12028	16002	13490	8500	7485	3379	1379	873
2008/2009	3346	10237	18527	21530	16800	10194	7863	4674	2401	2138

Figure 5.2 Excess mortality rates by calendar year interval among 64,836 HIV-infected patients initiating combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program 2003 – 2009 by CD4 cell count at therapy initiation.



No.								
2003/2004	994	840	1007	1088	1230	885	752	2629
2005/2007	10821	7076	7170	8292	6780	5146	3284	9017
2008/2009	20280	11809	11309	13419	10914	8750	5197	7207

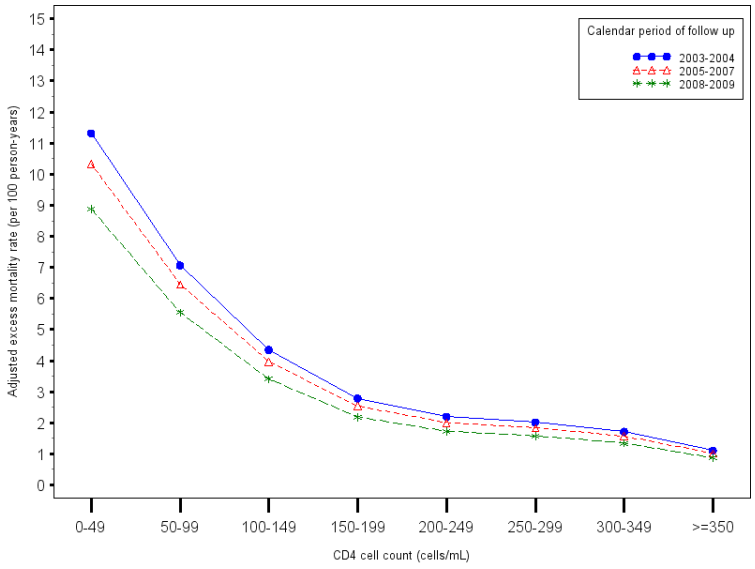
Figure 5.3 Adjusted excess mortality rates by calendar year interval among 64,836 HIV-infected patients initiating combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program 2003 – 2009 by age



No.										
2003/2004	50	364	1284	2201	1995	1488	1306	453	169	58
2005/2007	1139	4268	9724	12695	10708	6573	5903	2615	1067	617
2008/2009	2925	9040	16228	18590	14339	8496	6540	3850	1964	1699

Note: NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine. The adjusted excess mortality rates were estimated from one model including calendar year, age, sex, HIV exposure category, CD4 count, area of residence, health care setting, number of baseline symptoms and initial antiretroviral therapy regimen.

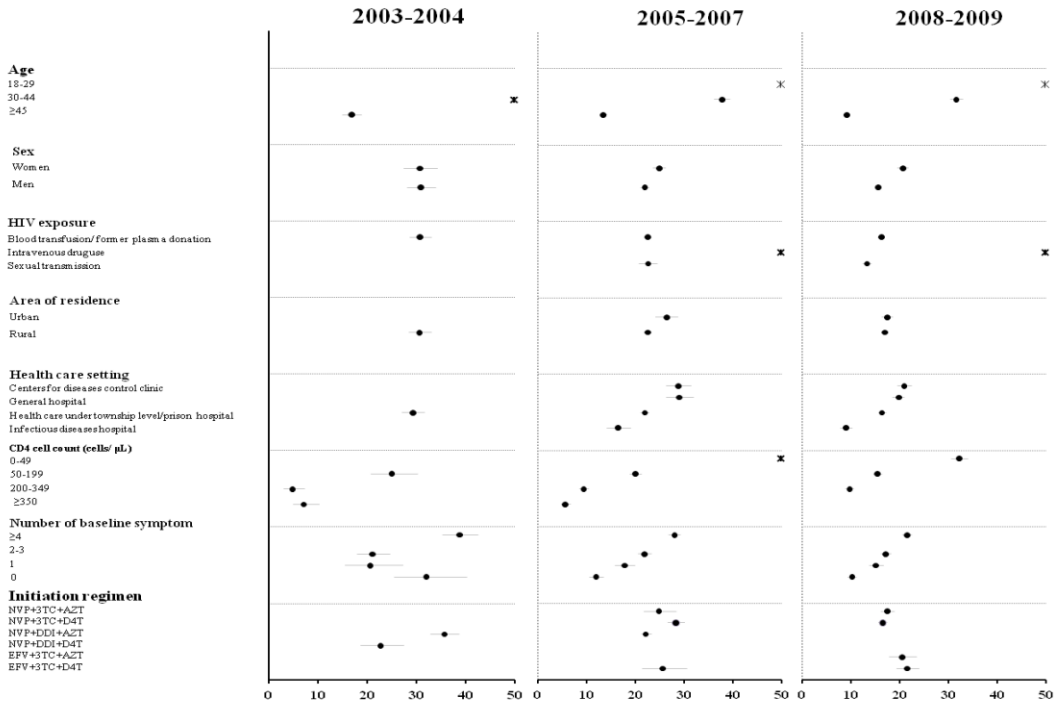
Figure 5.4 Adjusted excess mortality rates by calendar year interval among 64,836 HIV-infected patients initiating combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program 2003 – 2009 by CD4 count at therapy initiation.



No.								
2003/2004	348	268	263	298	272	220	183	294
2005/2007	2200	1566	1466	1485	1107	897	513	602
2008/2009	3295	2593	2394	2467	2058	1756	1300	906

Note: NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine. The adjusted excess mortality rates were estimated from one model including calendar year, age, sex, HIV exposure category, CD4 count, area of residence, health care setting, number of baseline symptoms and initial antiretroviral therapy regimen.

Figure 5.5 Standardized mortality ratios among 64,836 HIV-infected patients initiating combination antiretroviral therapy stratified by patient characteristics, the China National Free Antiretroviral Treatment Program 2003-2009 †



Note: NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; d4T=stavudine; DDI=didanosine; EFV=efavirenz. †Standardized mortality ratios are not depicted for strata with fewer than 1000 patients, including in 2003/2004: age 18-29, Intravenous drugs use, sexual transmission, urban, general hospital, infectious diseases hospital, centers for diseases control clinic, CD4 count 0-49 cells/ μL, NVP+3TC+AZT, NVP+3TC+D4T EFV+3TC+AZT, EFV+3TC+D4T and other regimens; in 2005-2007: NVP+DDI+D4T, EFV+3TC+AZT and other regimens; in 2008/2009: CD4 count ≥350cells/ μL, NVP+DDI+AZT, NVP+DDI+D4T, and other regimens.

* Standardized mortality ratios for 2003/2004 were: age 30-44 54.1 [95% confidence interval (CI): 49.2 - 59.4]; for 2005-2007: age18-29 114.9 (95CI%: 102.0 - 129.5), intravenous drugs use 47.6 (95% CI: 41.5 - 54.5), CD4 count 0-49 cells/ μL 61.3 (95%CI: 57.8 - 64.9); for 2008/2009: age 18-29 70.8 (95CI%: 63.5 - 79.0), intravenous drugs use 53.9 (95% CI: 50.1 - 57.9).

VI. CONCLUSIONS

Summary of findings

This study is one of the largest to evaluate retention in HIV care and the only study to date to be carried out in China. An improved understanding of attrition and factors associated with risk of attrition could help direct future public health interventions to maintain retention in treatment and thereby improve patient clinical outcomes. Also, this study assessed changes of difference between the mortality of HIV-infected patients initiating cART with the mortality in general population across calendar time. The ability to contrast mortality rates among HIV-infected patients receiving cART with general Chinese mortality data allowed us to generate data relevant to HIV care providers and policy makers in China as they evaluate cART provision in China and the future allocation of health care resource.

We observed a cumulative probability of attrition from cART initiation of 9% at 12 months, 16% at 24 months and 24% at 60 months among 67,732 HIV-infected patients initiating cART. Factors associated with attrition included younger age, being male and being single or divorced. Patients with higher CD4 counts at cART initiation were more likely to be lost to HIV care. The proportion of patients remaining in HIV care increased in more recent calendar years and among patients who initiated more modern cART regimens. Patients who received HIV care at larger and more centralized health care settings were more likely to be lost to care than patients receiving care at village level clinics. Using different time intervals

to define attrition, including 180, 270 and 360 days from last observation, our results were consistent irrespective of the definition of attrition we applied.

Among over 64,000 HIV-infected patients initiating cART in China we found both observed and excess mortality rates decreased more than 30% from 2003 to 2009. Also, the standardized mortality ratio decreased from 30.8 (95% CI: 28.6, 33.1) to 17.0 (95% CI: 16.5, 17.6) from 2003/2004 to 2008/2009. The decreases in excess mortality rates and SMRs across calendar time were largely consistent within all patient demographic and clinical characteristics. In a multivariable analysis, the high risk of excess mortality was statistically associated with older age, male, being IDU, living in rural area, lower CD4 counts, higher numbers of symptoms and earlier years of staring cART

Limitations

This study has some limitations. One limitation is the lack of some covariates, including date of HIV infection, HIV RNA viral load at enrollment and drug resistance results, which may impact the effect of the main exposure and other measured confounders on the association of attrition in care and excess mortality. Also, we were unable to evaluate the effect of longitudinal CD4 counts or HIV RNA levels on retention as these data were not available in the early years of the NFATP program.

Secondly, we were not able to link the study population with national death registries, nor was there active follow-up of patients lost to care. Thus, our estimate of attrition may be overestimated due to the patients who died but their death was not reported to the clinic. We may also be underestimating the observed mortality rates if unobserved mortality was substantial. Given that attrition from HIV care was greater among patients with higher CD4

cell counts we do not expect that mortality was strongly associated with attrition and censoring.

Thirdly, our findings of attrition in care may not generalize to clinics in other areas of the world because the unique contextual frames of the Chinese NFATP program. For example, as part of NFATP all patients received free antiretroviral therapy as well as other needed HIV care. Findings from other settings showed that retention increases in programs that offer free ART.

Finally, for the estimates of excess mortality, we were unable to match on some characteristics which were different from the general population such as a higher prevalence of other comorbidities (e.g., Hepatitis B or C infection).

Implications

This study describing attrition from HIV care provides relevant information to guide local physicians and health workers with respect to the best practices in monitoring treatment of patients receiving routine clinic care. It also supports policy makers to develop better strategies to control and minimize factors associated with attrition, as they may lead to treatment failure including drug resistance, toxicity and poor clinical response. Retention in HIV care is essential for optimizing individual and public health outcomes. Attrition, even the degree observed in our study, can lead to premature morbidity and mortality, and possibly affect further transmission of HIV and HIV resistant drug variants. Effective strategies to promote retention in HIV care programs are needed. In China intervention strategies may include focusing particularly on younger and male patients and those with higher CD4 counts at therapy initiation.

The results of the change in long-term excess mortality among HIV-infected patients receiving cART can provide information on the public health effectiveness of medical regimens after taking into account factors related to toxicity, drug resistance and adherence. Meanwhile, demonstrating the excess mortality trends can be useful for health resource allocation and optimization of current therapeutic regimens. Among HIV-infected patients receiving cART through the Chinese NFATP we have observed substantial decreases in excess mortality in comparison to the general population from 2003 to 2009. It is anticipated further reductions will be achieved as NFATP is able to provide more efficacious first and second line cART regimens. Our results indicate that further reductions in mortality will also entail identifying patients early after HIV-infection and linking then with HIV care.

Future plans

We were unable to link the study population with national death registries, such as the Death Cause Register System of the Chinese Ministry of Health. Future work with this cohort of patients would benefit from a linkage between these two systems to identify any deaths that may not have been captured by local health workers. It may also be beneficial to initiate an active tracing system among patients who are lost to HIV care. Given this is a labor and cost intensive type of intervention, this work may be best focused among the most at risk patients. It may be possible to undertake a smaller study where a random group of patients lost to HIV care are actively traced as has been done previously in other areas of the world [46]. This information can then be used to better understand the reasons for attrition from HIV care, including the risk of death among these patients.

Finally, it may also be useful to use modeling strategies to estimate the duration of infection among HIV-infected patients as they enter HIV care through the NFATP program in China. If this data can be accurately estimated then it may provide relevant information on delays for accessing HIV care and may be used in additional analyses evaluating HIV prognosis or response to therapy in this population. Finally, a high priority for future work is implementing routine CD4 cell count and HIV RNA level testing both at cART initiation and longitudinally. Although resource intensive and challenging to implement especially in rural and isolated areas of China, this data would likely prove invaluable to HIV care providers as well as future projects evaluating response to cART therapy in China.

Appendix A

Additional tables

Table A.1 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (according to the definition of attrition as 180 days)

Characteristic	**Unadjusted HR (95% CI)**	***Adjusted HR (95% CI)**
Age (years)		
18-29	1.34 (1.27 - 1.41)	1.11 (1.04 - 1.18)
30-44	1.22 (1.18 - 1.28)	0.98 (0.93 - 1.03)
≥45	1	1
Gender		
Male	1.18 (1.14 - 1.22)	1.06 (1.02 - 1.11)
Female	1	1
Marital status		
Divorced	1.28 (1.20 - 1.36)	1.25 (1.16 - 1.34)
Single	1.39 (1.33 - 1.45)	1.20 (1.13 - 1.26)
Widowed	0.97 (0.91 - 1.03)	1.06 (0.98 - 1.15)
Married	1	1
HIV exposure		
Blood transfusion/former plasma donation	1.08 (1.03 - 1.12)	0.84 (0.77 - 0.91)
Intravenous drug use	1.98 (1.90 - 2.06)	1.67 (1.59 - 1.75)
Homosexual transmission	0.51 (0.44 - 0.58)	0.53 (0.46 - 0.62)
Heterosexual transmission	1	1
Area of residence		
Eastern region	0.79 (0.76 - 0.82)	1.01 (0.95 - 1.09)
Central region	0.88 (0.83 - 0.92)	0.77 (0.71 - 0.83)
Western region	1	1
Health care setting		
General hospital	2.11 (1.87 - 2.38)	1.26 (1.06 - 1.48)
Infectious diseases hospital	1.56 (1.37 - 1.76)	1.00 (0.84 - 1.19)
Centers for diseases control clinic	1.49 (1.31 - 1.69)	1.04 (0.88 - 1.22)
Health care center at township level	1.88 (1.65 - 2.13)	1.37 (1.17 - 1.61)
Prison hospital	4.36 (3.68 - 5.15)	2.32 (1.89 - 2.86)
Village clinic	1	1
CD4 cell count (cells/ μL)		
≥350	1.47 (1.34 - 1.61)	1.57 (1.40 - 1.76)
200-349	1.08 (1.03 - 1.13)	1.04 (0.99 - 1.11)
50-199	1.03 (0.99 - 1.08)	1.00 (0.95 - 1.05)
0-49	1	1

Table A.1 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (according to the definition of attrition as 180 days) (continued)

Characteristic	**Unadjusted HR (95% CI)**	***Adjusted HR (95% CI)**
Hemoglobin (g/L)		
0-79	1.18 (1.08 - 1.29)	1.19 (1.07 - 1.31)
≥80	1	1
ALT (U/L)		
≥100	1.24 (1.15 - 1.35)	
0-99	1	
Number of baseline symptom		
≥4	1.12 (1.08 - 1.17)	1.05 (1.00 - 1.11)
2-3	1.01 (0.96 - 1.05)	0.97 (0.92 - 1.03)
1	1.03 (0.98 - 1.09)	0.99 (0.93 - 1.05)
0	1	1
Initiation cART regimen		
NVP+3TC+AZT	0.93 (0.88 - 1.00)	0.96 (0.89 - 1.03)
NVP+3TC+D4T	1.05 (0.99 - 1.12)	0.94 (0.88 - 1.01)
NVP+DDI+AZT	1.56 (1.43 - 1.70)	1.53 (1.34 - 1.74)
NVP+DDI+D4T	1.86 (1.71 - 2.03)	0.96 (0.83 - 1.10)
EFV+3TC+AZT	1	1
EFV+3TC+D4T	0.96 (0.89 - 1.04)	0.89 (0.81 - 0.97)
Other regimens	1.55 (1.41 - 1.71)	1.31 (1.16 - 1.48)
Year of cART initiation		
2003-2004	3.54 (3.31 - 3.79)	4.23 (3.76 - 4.75)
2005-2006	2.13 (2.02 - 2.24)	2.14 (2.01 - 2.27)
2007-2008	1.38 (1.31 - 1.44)	1.32 (1.25 - 1.39)
2009-2010	1	1

*****Adjusted hazard ratios are based on one model including all characteristics listed in column except ALT. Note: HR = hazard ratio; 95% CI = 95% Confidence Interval; ALT=alanine aminotransferase; cART=Combination Antiretroviral Therapy; NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; D4T=stavudine; DDI=didanosine; EFV=efavirenz.

Table A.2 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (according to the definition of attrition as 270 days)

Characteristic	Unadjusted HR (95% CI)	*Adjusted HR (95% CI)
Characteristic		
Age (years)	1.55 (1.45 - 1.66)	1.07 (0.98 - 1.16)
18-29	1.26 (1.19 - 1.33)	0.90 (0.84 - 0.97)
30-44	1	1
≥45		
Gender	1.33 (1.27 - 1.39)	1.10 (1.04 - 1.17)
Male	1	1
Female		
Marital status	1.48 (1.37 - 1.61)	1.35 (1.24 - 1.48)
Divorced	1.74 (1.65 - 1.83)	1.33 (1.24 - 1.42)
Single	0.97 (0.89 - 1.04)	1.16 (1.05 - 1.29)
Widowed	1	1
Married		
HIV exposure	0.78 (0.73 - 0.83)	0.71 (0.63 - 0.80)
Blood transfusion/former plasma donation	2.26 (2.15 - 2.38)	1.92 (1.80 - 2.05)
Intravenous drug use	0.50 (0.41 - 0.60)	0.46 (0.37 - 0.56)
Homosexual transmission	1	1
Heterosexual transmission		
Area of residence	0.93 (0.87 - 0.99)	1.04 (0.95 - 1.13)
Eastern region	0.57 (0.54 - 0.60)	0.67 (0.60 - 0.74)
Central region	1	1
Western region		
Health care setting	2.70 (2.26 - 3.23)	1.12 (0.87 - 1.43)
General hospital	2.30 (1.91 - 2.76)	1.11 (0.86 - 1.42)
Infectious diseases hospital	1.68 (1.40 - 2.02)	0.97 (0.76 - 1.24)
Centers for diseases control clinic	1.76 (1.46 - 2.12)	1.26 (0.99 - 1.60)
Health care center at township level	6.56 (5.24 - 8.22)	2.27 (1.70 - 3.02)
Prison hospital	1	1
Village clinic		
CD4 cell count (cells/ μL)	1.65 (1.47 - 1.86)	1.83 (1.59 - 2.10)
≥350	1.15 (1.08 - 1.22)	1.09 (1.01 - 1.17)
200-349	1.00 (0.94 - 1.06)	0.98 (0.91 - 1.04)
50-199	1	1
0-49		
Hemoglobin (g/L)	1.25 (1.12 - 1.40)	1.27 (1.11 - 1.44)
0-79	1	1
≥80		

Table A.2 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (according to the definition of attrition as 270 days) (continued)

Characteristic	Unadjusted HR (95% CI)	*Adjusted HR (95% CI)
ALT (U/L)	1.28 (1.15 - 1.42)	
≥100	1	
0-99		
Number of baseline symptom	1.04 (0.99 - 1.10)	
≥4	0.95 (0.89 - 1.01)	
2-3	0.95 (0.89 - 1.02)	
1	1	
0		
Initiation cART regimen	0.88 (0.81 - 0.95)	0.94 (0.86 - 1.03)
NVP+3TC+AZT	0.84 (0.78 - 0.91)	0.82 (0.75 - 0.90)
NVP+3TC+D4T	1.05 (0.93 - 1.18)	1.57 (1.30 - 1.88)
NVP+DDI+AZT	1.14 (1.01 - 1.28)	0.97 (0.81 - 1.18)
NVP+DDI+D4T	1	1
EFV+3TC+AZT	0.87 (0.79 - 0.97)	0.83 (0.74 - 0.93)
EFV+3TC+D4T	1.25 (1.10 - 1.41)	1.34 (1.15 - 1.56)
Other regimens		
Year of cART initiation	2.11 (1.92 - 2.33)	3.04 (2.58 - 3.58)
2003-2004	1.51 (1.41 - 1.62)	1.54 (1.42 - 1.68)
2005-2006	1.26 (1.18 - 1.34)	1.22 (1.14 - 1.31)
2007-2008	1	1

*Adjusted hazard ratios are based on one model including all characteristics listed in column except ALT. Note: HR = hazard ratio; 95% CI = 95% Confidence Interval; ALT=alanine aminotransferase; cART=Combination Antiretroviral Therapy; NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; D4T=stavudine; DDI=didanosine; EFV=efavirenz.

Table A.3 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (according to the definition of attrition as 360 days)

Characteristic	Unadjusted HR (95% CI)	*Adjusted HR (95% CI)
Age (years)		
18-29	1.63 (1.51 - 1.76)	1.03 (0.94 - 1.14)
30-44	1.28 (1.20 - 1.36)	0.88 (0.81 - 0.96)
≥45	1	1
Gender		
Male	1.36 (1.29 - 1.43)	1.11 (1.03 - 1.19)
Female	1	1
Marital status		
Divorced	1.57 (1.43 - 1.72)	1.41 (1.28 - 1.57)
Single	1.87 (1.76 - 1.98)	1.37 (1.28 - 1.48)
Widowed	0.95 (0.86 - 1.05)	1.17 (1.04 - 1.32)
Married	1	1
HIV exposure		
Blood transfusion/former plasma donation	0.65 (0.61 - 0.71)	0.62 (0.54 - 0.71)
Intravenous drug use	2.30 (2.17 - 2.43)	1.97 (1.83 - 2.12)
Homosexual transmission	0.53 (0.43 - 0.65)	0.49 (0.39 - 0.62)
Heterosexual transmission	1	1
Area of residence		
Eastern region	0.93 (0.86 - 1.00)	0.98 (0.89 - 1.08)
Central region	0.50 (0.47 - 0.53)	0.65 (0.58 - 0.74)
Western region	1	1
Health care setting		
General hospital	4.05 (3.18 - 5.16)	1.69 (1.19 - 2.40)
Infectious diseases hospital	3.71 (2.90 - 4.74)	1.82 (1.28 - 2.59)
Centers for diseases control clinic	2.47 (1.93 - 3.16)	1.51 (1.06 - 2.13)
Health care center at township level	2.28 (1.77 - 2.93)	1.81 (1.28 - 2.56)
Prison hospital	10.71 (8.07 - 14.22)	3.80 (2.59 - 5.58)
Village clinic	1	1
CD4 cell count (cells/ μL)		
≥350	1.73 (1.53 - 1.97)	2.07 (1.78 - 2.41)
200-349	1.13 (1.06 - 1.21)	1.06 (0.98 - 1.15)
50-199	0.94 (0.88 - 1.00)	0.93 (0.86 - 1.00)
0-49	1	1
Hemoglobin (g/L)		
0-79	1.34 (1.18 - 1.51)	1.33 (1.15 - 1.53)
≥80	1	1
ALT (U/L)		
≥100	1.30 (1.15 - 1.46)	
0-99	1	

Table A.3 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (according to the definition of attrition as 360 days) (continued)

Characteristic	Unadjusted HR (95% CI)	*Adjusted HR (95% CI)
Number of baseline symptom		
≥4	1.02 (0.96 - 1.09)	
2-3	0.94 (0.88 - 1.01)	
1	0.94 (0.86 - 1.01)	
0	1	
Initiation cART regimen		
NVP+3TC+AZT	0.83 (0.76 - 0.91)	0.93 (0.84 - 1.03)
NVP+3TC+D4T	0.77 (0.70 - 0.84)	0.79 (0.71 - 0.87)
NVP+DDI+AZT	0.82 (0.71 - 0.94)	1.45 (1.17 - 1.81)
NVP+DDI+D4T	0.97 (0.85 - 1.11)	1.01 (0.82 - 1.25)
EFV+3TC+AZT	1	1
EFV+3TC+D4T	0.83 (0.74 - 0.93)	0.79 (0.70 - 0.90)
Other regimens	1.21 (1.06 - 1.39)	1.44 (1.22 - 1.70)
Year of cART initiation		
2003-2004	1.84 (1.64 - 2.06)	2.79 (2.32 - 3.36)
2005-2006	1.36 (1.25 - 1.48)	1.38 (1.25 - 1.52)
2007-2008	1.20 (1.11 - 1.29)	1.17 (1.08 - 1.27)
2009-2010	1	1

*****Adjusted hazard ratios are based on one model including all characteristics listed in column except ALT. Note: HR = hazard ratio; 95% CI = 95% Confidence Interval; ALT=alanine aminotransferase; cART=Combination Antiretroviral Therapy; NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; D4T=stavudine; DDI=didanosine; EFV=efavirenz.

Table A.4 Comparison of Characteristics HIV-infected patients at combination antiretroviral therapy initiation between with and without follow-up, the China National Free Antiretroviral Treatment Program 2003 - 2010

Characteristic	With	Without	P value
Age (years)			
18-29	14,280 (17%)	648 (22%)	
30-44	45,089 (55%)	1,421 (49%)	
≥45	22,558 (28%)	827 (29%)	<.0001
Gender			
Female	29,743 (36%)	839 (29%)	
Male	52,180 (64%)	2,057 (71%)	<.0001
Marital status			
Single	13,381 (16%)	600 (21%)	
Married	55,932 (68%)	1,851 (64%)	
Divorced	6,006 (7%)	262 (9%)	
Widowed	6,399 (7%)	168 (6%)	<.0001
HIV exposure			
Blood transfusion/former plasma donation	15,725 (23%)	174 (6%)	
Intravenous drug use	15,974 (22%)	736 (27%)	
Homosexual transmission	4,204 (4%)	263 (10%)	
Heterosexual transmission	40,748 (51%)	1,556 (57%)	<.0001
Area of residence			
Eastern region	10,664 (13%)	678 (23%)	
Central region	24,416 (30%)	430 (15%)	
Western region	46,847 (57%)	1,788 (62%)	<.0001
Health care setting			
General hospital	33,081 (41%)	1,460 (51%)	
Infectious diseases hospital	14,917 (18%)	452 (16%)	
Centers for diseases control clinic	19,849 (24%)	768 (26%)	
Health care center at township level	10,524 (13%)	144 (5%)	
Village clinic	2,236 (3%)	16 (1%)	
Prison hospital	759 (1%)	42 (1%)	<.0001
CD4 cell counts (cells/ μL)			
0-49	20,604 (27%)	541 (20%)	
50-199	31,658 (41%)	926 (33%)	
200-349	22,805 (29%)	1,180 (43%)	
≥350	2,167 (3%)	107 (4%)	<.0001
Hemoglobin (g/L)			
0-79	3,029 (4%)	80 (3%)	
≥80	71,717(96%)	2,411 (97%)	0.04
ALT (U/L)			
≥100	2,852 (4%)	109 (4%)	
0-99	71,413 (96%)	2,466 (96%)	0.31

Table A.4 Comparison of Characteristics HIV-infected patients at combination antiretroviral therapy initiation between with and without follow-up, the China National Free Antiretroviral Treatment Program 2003 - 2010 (continued)

Characteristic	With	Without	P value
Number of baseline symptoms			
≥4	19,336 (24%)	303 (11%)	
2-3	17,391 (21%)	408 (14%)	
1	10,898 (13%)	323 (11%)	
0	34,302 (42%)	1,862 (64%)	<.0001
Initiation cART regimen			
NVP+3TC+AZT	28,485 (35%)	1,285 (44%)	
NVP+3TC+D4T	28,322 (35%)	700 (24%)	
NVP+DDI+AZT	2,618 (3%)	7 (0%)	
NVP+DDI+D4T	1,986 (2%)	15 (1%)	
EFV+3TC+AZT	9,613 (12%)	453 (16%)	
EFV+3TC+D4T	8,226 (10%)	304 (10%)	
Other regimens	2,677 (3%)	132 (5%)	<.0001
Year of cART initiation			
2003-2004	2,182 (3%)	14 (1%)	
2005-2006	9,880 (15%)	90 (3%)	
2007-2008	27,149 (40%)	249 (8%)	
2009-2010	28,521 (42%)	2543 (88%)	<.0001

Note ALT=alanine aminotransferase; cART=Combination Antiretroviral Therapy; NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; D4T=stavudine; DDI=didanosine; EFV=efavirenz;

Table A.5 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (including no follow up)

Characteristic	**Unadjusted HR (95% CI)**	***Adjusted HR (95% CI)**
Age (years)		
18-29	1.51 (1.42 -1.60)	1.10 (1.02 - 1.19)
30-44	1.28 (1.22 -1.35)	0.94 (0.89 - 1.01)
≥45	1	1
Gender		
Male	1.29 (1.24 - 1.34)	1.08 (1.02 - 1.14)
Female	1	1
Marital status		
Divorced	1.39 (1.30 - 1.50)	1.29 (1.18 - 1.40)
Single	1.61 (1.53 - 1.69)	1.25 (1.18 - 1.33)
Widowed	0.95 (0.88 - 1.03)	1.10 (1.00 - 1.21)
Married	1	1
HIV exposure		
Blood transfusion/former plasma donation	0.84 (0.79 - 0.88)	0.74 (0.67 - 0.83)
Intravenous drug use	2.18 (2.08 - 2.28)	1.85 (1.75 - 1.96)
Homosexual transmission	0.53 (0.46 - 0.62)	0.52 (0.44 - 0.62)
Heterosexual transmission	1	1
Area of residence		
Eastern region	0.92 (0.86 - 0.97)	1.04 (0.96 - 1.12)
Central region	0.62 (0.59 - 0.65)	0.68 (0.62 - 0.75)
Western region	1	1
Health care setting		
General hospital	2.55 (2.18 - 3.00)	1.20 (0.96 - 1.49)
Infectious diseases hospital	2.06 (1.75 - 2.43)	1.09 (0.87 - 1.36)
Centers for diseases control clinic	1.66 (1.41 - 1.95)	1.03 (0.83 - 1.28)
Health care center at township level	1.77 (1.50 - 2.09)	1.39 (1.12 - 1.72)
Prison hospital	5.91 (4.83 - 7.24)	2.35 (1.82 - 3.05)
Village clinic	1	1
CD4 counts (cells/ μL)		
≥350	1.57 (1.41 - 1.75)	1.75 (1.54 - 1.99)
200-349	1.13 (1.07 - 1.19)	1.07 (1.00 - 1.15)
50-199	1.01 (0.96 - 1.07)	1.00 (0.94 - 1.06)
0-49	1	1
Hemoglobin (g/L)		
0-79	1.22 (1.10 - 1.35)	1.22 (1.08 - 1.37)
≥80	1	1
ALT (U/L)		
≥100	1.27 (1.15 - 1.40)	
0-99	1	
Number of baseline symptom		
≥4	1.07 (1.02 - 1.12)	1.06 (1.00 - 1.13)
2-3	0.94 (0.89 - 1.00)	0.97 (0.91 - 1.04)
1	0.96 (0.90 - 1.02)	0.96 (0.89 - 1.03)
0	1	1

Table A.5 Clinical and demographic characteristics associated with attrition among HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2010 (including no follow up) (continued)

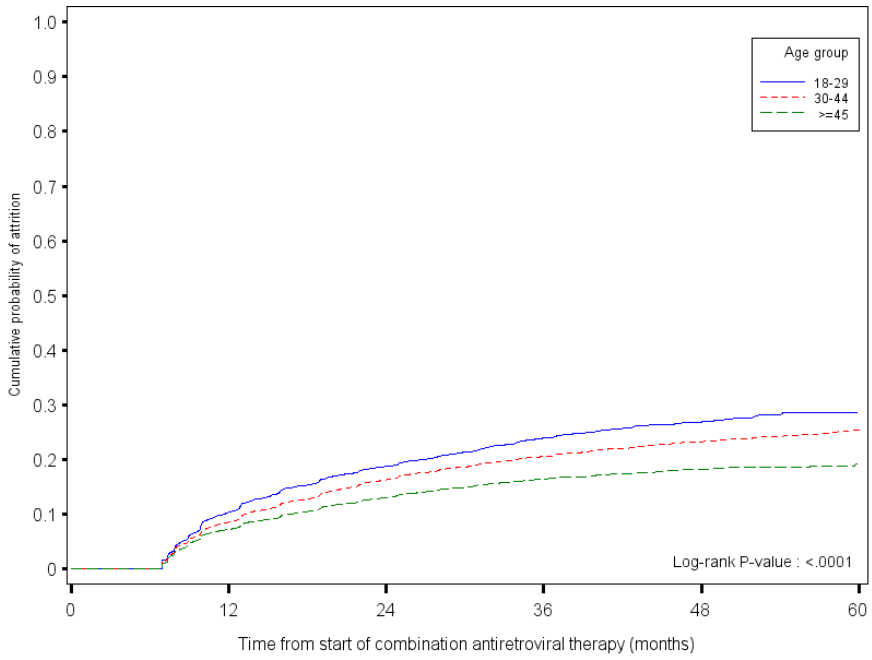
Characteristic	**Unadjusted HR (95% CI)**	***Adjusted HR (95% CI)**
Initiation cART regimen		
NVP+3TC+AZT	0.90 (0.84 - 0.97)	0.95 (0.88 - 1.03)
NVP+3TC+D4T	0.92 (0.85 - 0.98)	0.86 (0.79 - 0.93)
NVP+DDI+AZT	1.20 (1.08 - 1.34)	1.58 (1.34 - 1.86)
NVP+DDI+D4T	1.18 (1.06 - 1.32)	0.92 (0.77 - 1.10)
EFV+3TC+AZT	1	1
EFV+3TC+D4T	0.89 (0.81 - 0.98)	0.83 (0.75 - 0.92)
Other regimens	1.32 (1.18 - 1.47)	1.29 (1.13 - 1.49)
Year of cART initiation		
2003-2004	2.25 (2.06 - 2.46)	3.23 (2.79 - 3.74)
2005-2006	1.71 (1.61 - 1.82)	1.71 (1.58 - 1.84)
2007-2008	1.31 (1.24 - 1.38)	1.25 (1.18 - 1.33)
2009-2010	1	1

*****Adjusted hazard ratios are based on one model including all characteristics listed in column except ALT. Note: HR = hazard ratio; 95% CI = 95% Confidence Interval; ALT=alanine aminotransferase; cART=Combination Antiretroviral Therapy; NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; D4T=stavudine; DDI=didanosine; EFV=efavirenz.

Appendix B

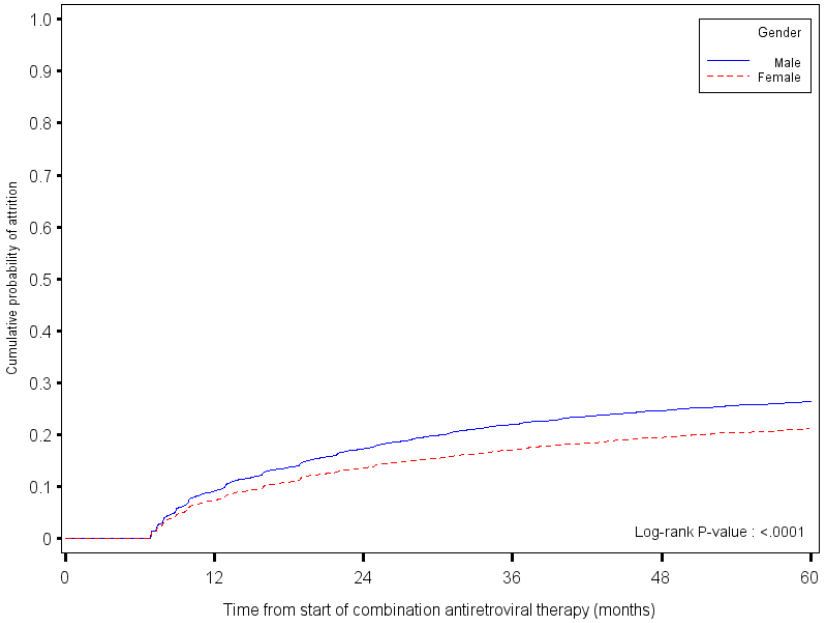
Additional figures

Figure A.1 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by age group



No. at risk						
18-29	11509	8309	4682	2440	1081	399
30-44	38200	27947	16550	9158	4338	1815
>=45	18023	12808	7210	3805	1828	792

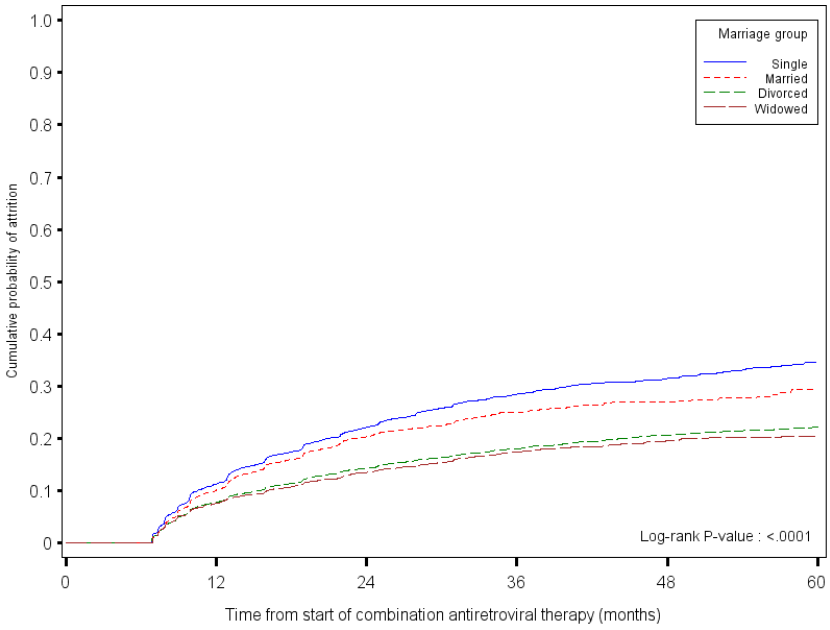
Figure A.2 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by gender group



No. at risk

Female	24930	18829	11443	6459	3102	1336
Male	42798	30231	16997	8943	4145	1670

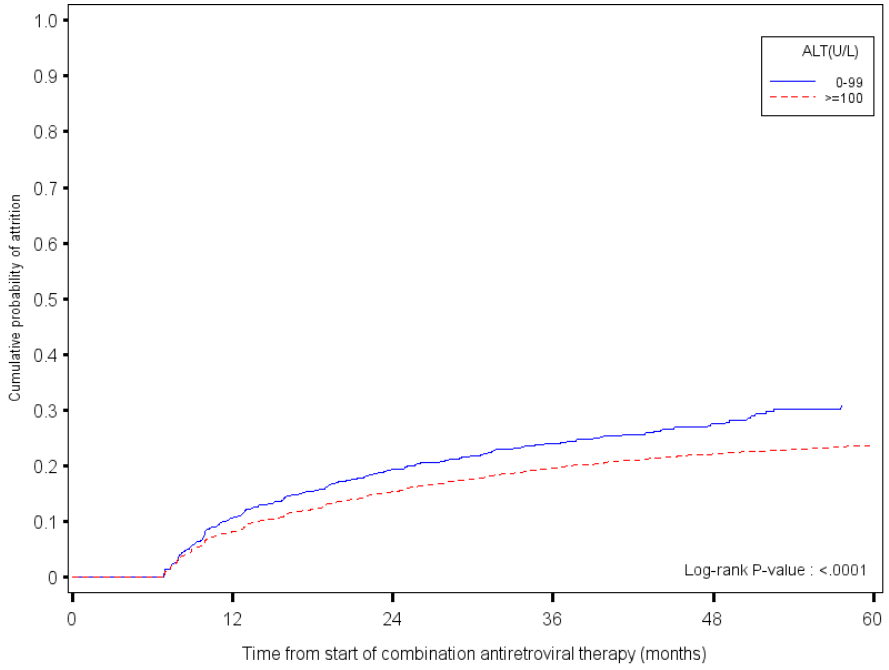
Figure A.3 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by marriage status group



No. at risk

Single	10875	7547	3970	1907	833	290
Divorced	4864	3296	1708	817	347	127
Married	46434	34143	20355	11349	5425	2312
Widowed	5399	3987	2384	1320	639	276

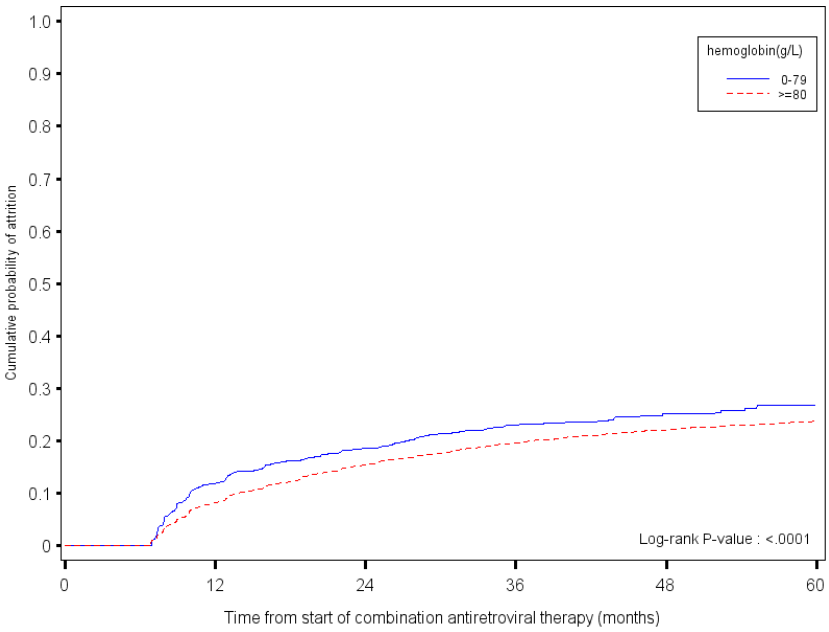
Figure A.4 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by alanine aminotransferase group



No. at risk

>=100	2421	1682	984	513	232	86
0-99	58875	43048	24636	13012	5884	2247

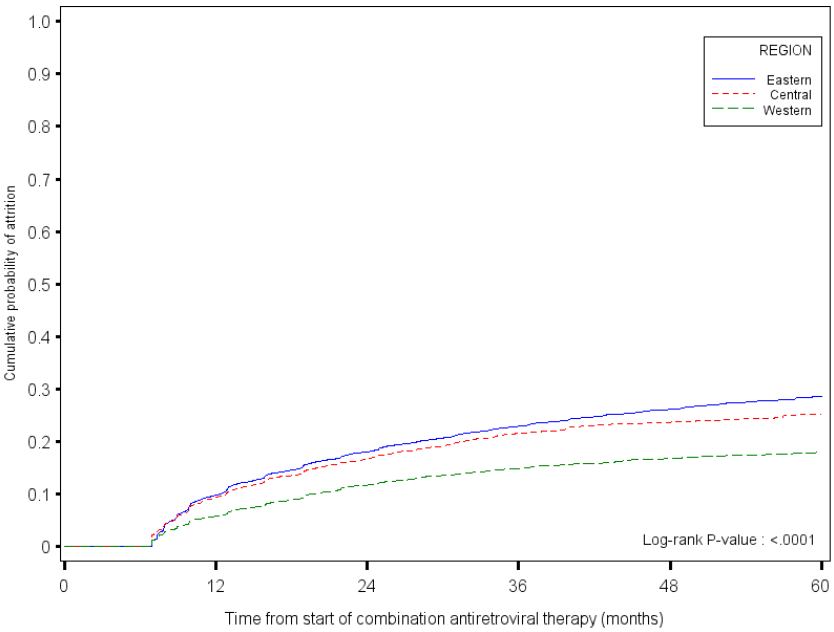
Figure A.5 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by hemoglobin group



No. at risk

0-79	2612	1524	934	553	273	91
≥80	59269	43626	25113	13329	6155	2448

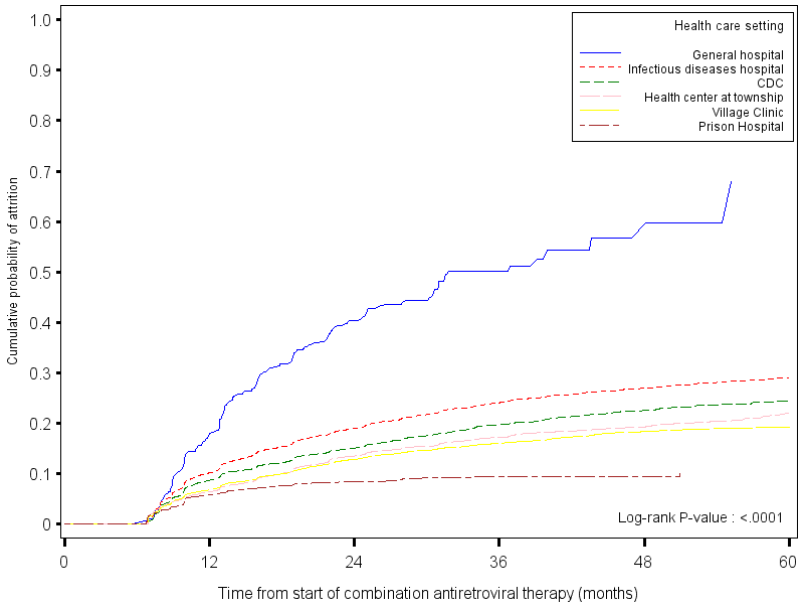
Figure A.6 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by region



No. at risk

Western area	38095	27111	15043	7304	3065	970
Eastern area	8359	5856	3077	1667	828	373
Central area	21278	16097	10322	6432	3354	1663

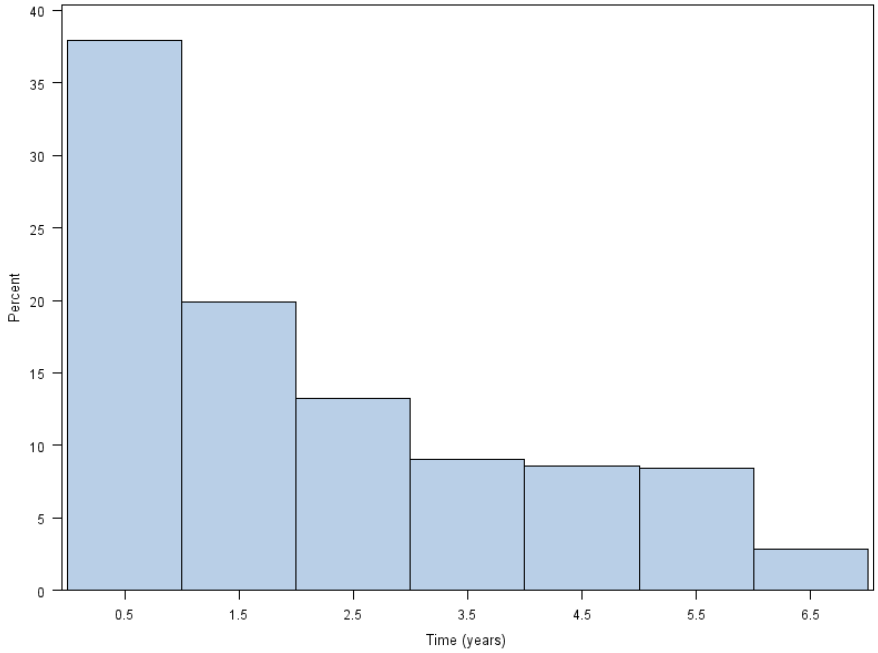
Figure A.7 Cumulative probability of attrition among HIV-infected patients who initiated combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program, 2003-2010 by health care setting.



No. at risk						
Prison hospital	646	445	172	47	14	4
General hospital	26801	18942	10402	4957	2050	725
Infectious diseases hospital	12321	8956	5145	2830	1338	472
CDC	16019	11479	6826	4094	2375	1238
Health center at township	9496	7252	4607	2793	1246	562
Village clinic	2000	1653	1099	598	206	3

Note: CDC= Centers for diseases control clinic.

Figure A.8 Distribution of follow up time among 64,836 HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 - 2009



REFERENCES

1. China. CMoHaUTGoHAi. A Joint Assessment of HIV/AIDS Prevention, Treatment, and Care in China: Beijing 2007. **2007**.

2. Wang L. Overview of the HIV/AIDS epidemic, scientific research and government responses in China. AIDS (London, England) **2007** Dec;21 Suppl 8:S3-7.

3. He N, Detels R. The HIV epidemic in China: history, response, and challenge. Cell research **2005** Nov-Dec;15(11-12):825-32.

4. Wu Z, Rou K, Cui H. The HIV/AIDS epidemic in China: history, current strategies and future challenges. AIDS Educ Prev **2004** Jun;16(3 Suppl A):7-17.

5. Sun X, Nan J, Guo Q. AIDS and HIV infection in China. AIDS (London, England) **1994**;8 Suppl 2:S55-9.

6. Su L, Du F. HIV infection and AIDS in China. American journal of public health **1998** Feb;88(2):307.

7. Zeng Y. HIV infection and AIDS in China. Archives of AIDS research **1992**;6(1-2):1-5.

8. Yu ES, Xie Q, Zhang K, Lu P, Chan LL. HIV infection and AIDS in China, 1985 through 1994. American journal of public health **1996** Aug;86(8):1116-22.

9. van Griensven F, de Lind van Wijngaarden JW. A review of the epidemiology of HIV infection and prevention responses among MSM in Asia. AIDS (London, England) Sep;24 Suppl 3:S30-40.

10. [National sentinel surveillance of HIV infection in China from 1995 to 1998]. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi **2000** Feb;21(1):7-9.

11. Jia Y, Lu F, Sun X, Vermund SH. Sources of data for improved surveillance of HIV/AIDS in China. The Southeast Asian journal of tropical medicine and public health **2007** Nov;38(6):1041-52.

12. Sun X, Wang N, Li D, et al. The development of HIV/AIDS surveillance in China. AIDS (London, England) **2007** Dec;21 Suppl 8:S33-8.

13. Detels R, Munoz A, McFarlane G, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. Jama **1998** Nov 4;280(17):1497-503.

14. Gange SJ, Barron Y, Greenblatt RM, et al. Effectiveness of highly active antiretroviral therapy among HIV-1 infected women. Journal of epidemiology and community health **2002** Feb;56(2):153-9.

15. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. The New England journal of medicine **1997** Sep 11;337(11):725-33.

16. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. The New England journal of medicine **1998** Mar 26;338(13):853-60.

17. ART-CC. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet **2008** Jul 26;372(9635):293-9.

18. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet **2006** Mar 11;367(9513):817-24.

19. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet **2003** Jul 5;362(9377):22-9.

20. Ahdieh-Grant L, Tarwater PM, Schneider MF, et al. Factors and temporal trends associated with highly active antiretroviral therapy discontinuation in the Women's Interagency HIV Study. Journal of acquired immune deficiency syndromes (1999) **2005** Apr 1;38(4):500-3.

21. Yuan Y, L'Italien G, Mukherjee J, Iloeje UH. Determinants of discontinuation of initial highly active antiretroviral therapy regimens in a US HIV-infected patient cohort. HIV medicine **2006** Apr;7(3):156-62.

22. Gerver SM, Chadborn TR, Ibrahim F, Vatsa B, Delpech VC, Easterbrook PJ. High rate of loss to clinical follow up among African HIV-infected patients attending a London clinic: a retrospective analysis of a clinical cohort. Journal of the International AIDS Society **2010**;13:29.

23. Kizito KW, Dunkley S, Kingori M, Reid T. Lost to follow up from tuberculosis treatment in an urban informal settlement (Kibera), Nairobi, Kenya: what are the rates and determinants? Transactions of the Royal Society of Tropical Medicine and Hygiene Oct 1.

24. Yu JK, Chen SC, Wang KY, et al. True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. Bulletin of the World Health Organization **2007** Jul;85(7):550-4.

25. MacPherson P, Moshabela M, Martinson N, Pronyk P. Mortality and loss to follow-up among HAART initiators in rural South Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene **2009** Jun;103(6):588-93.

26. Lawn SD, Myer L, Harling G, Orrell C, Bekker LG, Wood R. Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation. Clin Infect Dis **2006** Sep 15;43(6):770-6.

27. Lebouche B, Yazdanpanah Y, Gerard Y, et al. Incidence rate and risk factors for loss to follow-up in a French clinical cohort of HIV-infected patients from January 1985 to January 1998. HIV medicine **2006** Apr;7(3):140-5.

28. Chasombat S, McConnell MS, Siangphoe U, et al. National expansion of antiretroviral treatment in Thailand, 2000-2007: program scale-up and patient outcomes. Journal of acquired immune deficiency syndromes (1999) **2009** Apr 15;50(5):506-12.

29. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS medicine **2007** Oct 16;4(10):e298.

30. Ioannidis JP, Bassett R, Hughes MD, Volberding PA, Sacks HS, Lau J. Predictors and impact of patients lost to follow-up in a long-term randomized trial of immediate versus deferred antiretroviral treatment. J Acquir Immune Defic Syndr Hum Retrovirol **1997** Sep 1;16(1):22-30.

31. Nacher M, El Guedj M, Vaz T, et al. Risk factors for follow-up interruption of HIV patients in French Guiana. The American journal of tropical medicine and hygiene **2006** May;74(5):915-7.

32. Pacheco AG, Tuboi SH, May SB, et al. Temporal changes in causes of death among HIV-infected patients in the HAART era in Rio de Janeiro, Brazil. Journal of acquired immune deficiency syndromes (1999) **2009** Aug 15;51(5):624-30.

33. Toure S, Kouadio B, Seyler C, et al. Rapid scaling-up of antiretroviral therapy in 10,000 adults in Cote d'Ivoire: 2-year outcomes and determinants. AIDS (London, England) **2008** Apr 23;22(7):873-82.

34. Haddow LJ, Edwards SG, Sinka K, Mercey DE. Patients lost to follow up: experience of an HIV clinic. Sexually transmitted infections **2003** Aug;79(4):349-50.

35. Lanoy E, Mary-Krause M, Tattevin P, et al. Predictors identified for losses to follow-up among HIV-seropositive patients. Journal of clinical epidemiology **2006** Aug;59(8):829-35.

36. Yehia BR, Gebo KA, Hicks PB, et al. Structures of care in the clinics of the HIV Research Network. AIDS patient care and STDs **2008** Dec;22(12):1007-13.

37. Mocroft A, Kirk O, Aldins P, et al. Loss to follow-up in an international, multicentre observational study. HIV medicine **2008** May;9(5):261-9.

38. Ndiaye B, Ould-Kaci K, Salleron J, et al. Incidence rate and risk factors for loss to follow-up in HIV-infected patients from five French clinical centres in Northern France - January 1997 to December 2006. Antiviral therapy **2009**;14(4):567-75.

39. Maskew M, MacPhail P, Menezes C, Rubel D. Lost to follow up: contributing factors and challenges in South African patients on antiretroviral therapy. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde **2007** Sep;97(9):853-7.

40. Zachariah R, Van Engelgem I, Massaquoi M, et al. Payment for antiretroviral drugs is associated with a higher rate of patients lost to follow-up than those offered free-of-charge therapy in Nairobi, Kenya. Transactions of the Royal Society of Tropical Medicine and Hygiene **2008** Mar;102(3):288-93.

41. Cornell M, Myer L, Kaplan R, Bekker LG, Wood R. The impact of gender and income on survival and retention in a South African antiretroviral therapy programme. Trop Med Int Health **2009** Jul;14(7):722-31.

42. Kaplan R, Orrell C, Zwane E, Bekker LG, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. AIDS (London, England) **2008** Aug 20;22(13):1679-81.

43. Karcher H, Omondi A, Odera J, Kunz A, Harms G. Risk factors for treatment denial and loss to follow-up in an antiretroviral treatment cohort in Kenya. Trop Med Int Health **2007** May;12(5):687-94.

44. Lowrance DW, Ndamage F, Kayirangwa E, et al. Adult clinical and immunologic outcomes of the national antiretroviral treatment program in Rwanda during 2004-2005. Journal of acquired immune deficiency syndromes (1999) **2009** Sep 1;52(1):49-55.

45. Dalal RP, Macphail C, Mqhayi M, et al. Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in johannesburg, South Africa. Journal of acquired immune deficiency syndromes (1999) **2008** Jan 1;47(1):101-7.

46. Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. Jama **2008** Aug 6;300(5):506-7.

47. Brown DM, Thorne JE, Foster GL, et al. Factors affecting attrition in a longitudinal study of patients with AIDS. AIDS care **2006** Oct;18(7):821-9.

48. Coleman S, Boehmer U, Kanaya F, Grasso C, Tan J, Bradford J. Retention challenges for a community-based HIV primary care clinic and implications for intervention. AIDS patient care and STDs **2007** Sep;21(9):691-701.

49. Bisson GP, Gaolathe T, Gross R, et al. Overestimates of survival after HAART: implications for global scale-up efforts. PloS one **2008**;3(3):e1725.

50. Dumond JB, Yeh RF, Patterson KB, et al. Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis. AIDS (London, England) **2007** Sep 12;21(14):1899-907.

51. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS (London, England) **2008** Oct 1;22(15):1897-908.

52. Tuboi SH, Schechter M, McGowan CC, et al. Mortality during the first year of potent antiretroviral therapy in HIV-1-infected patients in 7 sites throughout Latin America and the Caribbean. Journal of acquired immune deficiency syndromes (1999) **2009** Aug 15;51(5):615-23.

53. Zhang F, Dou Z, Ma Y, et al. Five-year outcomes of the China National Free Antiretroviral Treatment Program. Annals of internal medicine **2009** Aug 18;151(4):241-51, W-52.

54. Lodwick RK, Sabin CA, Porter K, et al. Death rates in HIV-positive antiretroviral-naive patients with CD4 count greater than 350 cells per microL in Europe and North America: a pooled cohort observational study. Lancet Jul 31;376(9738):340-5.

55. Parkes-Ratanshi R, Bufumbo L, Nyanzi-Wakholi B, et al. Barriers to starting ART and how they can be overcome: individual and operational factors associated with early and late start of treatment. Trop Med Int Health Nov;15(11):1347-56.

56. Muchedzi A, Chandisarewa W, Keatinge J, et al. Factors associated with access to HIV care and treatment in a prevention of mother to child transmission programme in urban Zimbabwe. Journal of the International AIDS Society Oct 6;13(1):38.

57. Chileshe M, Bond VA. Barriers and outcomes: TB patients co-infected with HIV accessing antiretroviral therapy in rural Zambia. AIDS care;22 Suppl 1:51-9.

58. Njozing NB, Miguel SS, Tih PM, Hurtig AK. Assessing the accessibility of HIV care packages among tuberculosis patients in the Northwest Region, Cameroon. BMC public health;10:129.

59. Boyer S, Eboko F, Camara M, et al. Scaling up access to antiretroviral treatment for HIV infection: the impact of decentralization of healthcare delivery in Cameroon. AIDS (London, England) Jan;24 Suppl 1:S5-15.

60. Graham SM, Masese L, Gitau R, et al. Antiretroviral adherence and development of drug resistance are the strongest predictors of genital HIV-1 shedding among women initiating treatment. The Journal of infectious diseases Nov 15;202(10):1538-42.

61. Kelly A, Worth H, Man N, et al. Barriers and Facilitators for Adherence to Antiretroviral Therapy in Papua New Guinea. Current HIV research Oct 13.

62. Potchoo Y, Tchamdja K, Balogou A, Pitche VP, Guissou IP, Kassang EK. Knowledge and adherence to antiretroviral therapy among adult people living with HIV/AIDS treated in the health care centers of the association "Espoir Vie Togo" in Togo, West Africa. BMC clinical pharmacology;10:11.

63. Hegazi A, Bailey RL, Ahadzie B, Alabi A, Peterson K. Literacy, education and adherence to antiretroviral therapy in The Gambia. AIDS care Nov;22(11):1340-5.

64. Polejack L, Seidl EM. [Monitoring and evaluation of adherence to ARV treatment for HIV/aids: challenges and possibilities]. Ciencia & saude coletiva Jun;15 Suppl 1:1201-8.

65. Merten S, Kenter E, McKenzie O, Musheke M, Ntalasha H, Martin-Hilber A. Patient-reported barriers and drivers of adherence to antiretrovirals in sub-Saharan Africa: a meta-ethnography. Trop Med Int Health Jun;15 Suppl 1:16-33.

66. Bianco JA, Heckman TG, Sutton M, Watakakosol R, Lovejoy T. Predicting Adherence to Antiretroviral Therapy in HIV-Infected Older Adults: The Moderating Role of Gender. AIDS and behavior Jul 15.

67. Aaron E, Kempf MC, Criniti S, et al. Adverse events in a cohort of HIV infected pregnant and non-pregnant women treated with nevirapine versus non-nevirapine antiretroviral medication. PloS one;5(9):e12617.

68. Diop-Ndiaye H, Toure-Kane C, Leye N, et al. Antiretroviral drug resistance mutations in antiretroviral-naive patients from Senegal. AIDS research and human retroviruses Oct;26(10):1133-8.

69. Hamers RL, Siwale M, Wallis CL, et al. HIV-1 drug resistance mutations are present in six percent of persons initiating antiretroviral therapy in Lusaka, Zambia. Journal of acquired immune deficiency syndromes (1999) Sep 1;55(1):95-101.

70. Castro E, Khonkarly M, Ciuffreda D, et al. HIV-1 Drug Resistance Transmission Networks in Southwest Switzerland. AIDS research and human retroviruses Sep 23.

71. Toledo PV, Carvalho DS, Romagnoli L, et al. HIV-1 genotypic resistance profile of patients failing antiretroviral therapy in Parana, Brazil. Braz J Infect Dis Aug;14(4):360-71.

72. Krentz HB, Kliewer G, Gill MJ. Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. HIV medicine **2005** Mar;6(2):99-106.

73. Palella FJ, Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. Journal of acquired immune deficiency syndromes (1999) **2006** Sep;43(1):27-34.

74. Perez-Hoyos S, Ferreros I, del Amo J, et al. Survival and progression to AIDS in a seroconverter cohort in the post-highly active antiretroviral therapy era: effectiveness goes on. AIDS (London, England) **2006** Jan 9;20(2):289-91.

75. Porter K, Babiker A, Bhaskaran K, et al. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. Lancet **2003** Oct 18;362(9392):1267-74.

76. Lee LM, Karon JM, Selik R, Neal JJ, Fleming PL. Survival after AIDS diagnosis in adolescents and adults during the treatment era, United States, 1984-1997. Jama **2001** Mar 14;285(10):1308-15.

77. McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. Adult/Adolescent Spectrum of Disease Group. AIDS (London, England) **1999** Sep 10;13(13):1687-95.

78. Pezzotti P, Napoli PA, Acciai S, et al. Increasing survival time after AIDS in Italy: the role of new combination antiretroviral therapies. Tuscany AIDS Study Group. AIDS (London, England) **1999** Feb 4;13(2):249-55.

79. Schwarcz SK, Hsu LC, Vittinghoff E, Katz MH. Impact of protease inhibitors and other antiretroviral treatments on acquired immunodeficiency syndrome survival in San Francisco, California, 1987-1996. American journal of epidemiology **2000** Jul 15;152(2):178-85.

80. Couzigou C, Semaille C, Le Strat Y, et al. Differential improvement in survival among patients with AIDS after the introduction of HAART. AIDS care **2007** Apr;19(4):523-31.

81. Dore GJ, Li Y, McDonald A, Ree H, Kaldor JM. Impact of highly active antiretroviral therapy on individual AIDS-defining illness incidence and survival in Australia. Journal of acquired immune deficiency syndromes (1999) **2002** Apr 1;29(4):388-95.

82. Fordyce EJ, Singh TP, Nash D, Gallagher B, Forlenza S. Survival rates in NYC in the era of combination ART. Journal of acquired immune deficiency syndromes (1999) **2002** May 1;30(1):111-8.

83. Nash D, Katyal M, Shah S. Trends in predictors of death due to HIV-related causes among persons living with AIDS in New York City: 1993-2001. J Urban Health **2005** Dec;82(4):584-600.

84. Smit C, Geskus R, Uitenbroek D, et al. Declining AIDS mortality in Amsterdam: contributions of declining HIV incidence and effective therapy. Epidemiology (Cambridge, Mass **2004** Sep;15(5):536-42.

85. Sieleunou I, Souleymanou M, Schonenberger AM, Menten J, Boelaert M. Determinants of survival in AIDS patients on antiretroviral therapy in a rural centre in the Far-North Province, Cameroon. Trop Med Int Health **2009** Jan;14(1):36-43.

86. Etard JF, Ndiaye I, Thierry-Mieg M, et al. Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. AIDS (London, England) **2006** May 12;20(8):1181-9.

87. Zachariah R, Harries K, Moses M, et al. Very early mortality in patients starting antiretroviral treatment at primary health centres in rural Malawi. Trop Med Int Health **2009** Jul;14(7):713-21.

88. Johannessen A, Naman E, Ngowi BJ, et al. Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania. BMC infectious diseases **2008**;8:52.

89. Bussmann H, Wester CW, Ndwapi N, et al. Five-year outcomes of initial patients treated in Botswana's National Antiretroviral Treatment Program. AIDS (London, England) **2008** Nov 12;22(17):2303-11.

90. Severe P, Leger P, Charles M, et al. Antiretroviral therapy in a thousand patients with AIDS in Haiti. The New England journal of medicine **2005** Dec 1;353(22):2325-34.

91. Weidle PJ, Malamba S, Mwebaze R, et al. Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. Lancet **2002** Jul 6;360(9326):34-40.

92. Coetzee D, Hildebrand K, Boulle A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. AIDS (London, England) **2004** Apr 9;18(6):887-95.

93. Stringer JS, Zulu I, Levy J, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. Jama **2006** Aug 16;296(7):782-93.

94. Silverberg MJ, Leyden W, Quesenberry CP, Jr., Horberg MA. Race/ethnicity and risk of AIDS and death among HIV-infected patients with access to care. Journal of general internal medicine **2009** Sep;24(9):1065-72.

95. Taiwo BO, Li X, Palella F, et al. Higher risk of AIDS or death in patients with lower CD4 cell counts after virally suppressive HAART. HIV medicine **2009** Nov;10(10):657-60.

96. Ojikutu BO, Zheng H, Walensky RP, et al. Predictors of mortality in patients initiating antiretroviral therapy in Durban, South Africa. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde **2008** Mar;98(3):204-8.

97. Lawn SD, Little F, Bekker LG, et al. Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. AIDS (London, England) **2009** Jan 28;23(3):335-42.

98. Russell EC, Charalambous S, Pemba L, Churchyard GJ, Grant AD, Fielding K. Low haemoglobin predicts early mortality among adults starting antiretroviral therapy in an HIV care programme in South Africa: a cohort study. BMC public health;10:433.

99. Zachariah R, Fitzgerald M, Massaquoi M, et al. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. AIDS (London, England) **2006** Nov 28;20(18):2355-60.

100. May M, Boulle A, Phiri S, et al. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. Lancet **2010** Aug 7;376(9739):449-57.

101. Pezzotti P, d'Arminio Monforte A, Bugarini R, et al. Antiretroviral therapy in HIV-infected individuals in clinical practice: are the criteria for initiating and choosing the type of drug regimen based only on immunologic and virologic values? European journal of epidemiology **2000**;16(10):919-26.

102. ART-CC, Lanoy E, May M, et al. Prognosis of patients treated with cART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements. AIDS (London, England) **2009** Oct 23;23(16):2199-208.

103. ART-CC. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet **2009** Apr 18;373(9672):1352-63.

104. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. The New England journal of medicine **2009** Apr 30;360(18):1815-26.

105. Deeks SG, Gange SJ, Kitahata MM, et al. Trends in multidrug treatment failure and subsequent mortality among antiretroviral therapy-experienced patients with HIV infection in North America. Clin Infect Dis **2009** Nov 15;49(10):1582-90.

106. van Sighem A, Danner S, Ghani AC, Gras L, Anderson RM, de Wolf F. Mortality in patients with successful initial response to highly active antiretroviral therapy is still higher than in non-HIV-infected individuals. Journal of acquired immune deficiency syndromes (1999) **2005** Oct 1;40(2):212-8.

107. Colebunders R, Schrooten W, Dreezen C, et al. Antiretroviral treatments used among adults with HIV infection in Europe. AIDS care **2001** Feb;13(1):5-14.

108. Cook JA, Cohen MH, Grey D, et al. Use of highly active antiretroviral therapy in a cohort of HIV-seropositive women. American journal of public health **2002** Jan;92(1):82-7.

109. Hsu LC, Vittinghoff E, Katz MH, Schwarcz SK. Predictors of use of highly active antiretroviral therapy (HAART) among persons with AIDS in San Francisco, 1996-1999. Journal of acquired immune deficiency syndromes (1999) **2001** Dec 1;28(4):345-50.

110. Keruly JC, Conviser R, Moore RD. Association of medical insurance and other factors with receipt of antiretroviral therapy. American journal of public health **2002** May;92(5):852-7.

111. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Statistics in medicine **2004** Jan 15;23(1):51-64.

112. Henson DE, Ries LA. The relative survival rate. Cancer **1995** Nov 15;76(10):1687-8.

113. Roy P, Vaughan Hudson G, Vaughan Hudson B, Esteve J, Swerdlow AJ. Long-term survival in Hodgkin's disease patients. A comparison of relative survival in patients in trials and those recorded in population-based cancer registries. Eur J Cancer **2000** Feb;36(3):384-9.

114. Bhaskaran K, Hamouda O, Sannes M, et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. Jama **2008** Jul 2;300(1):51-9.

115. Brinkhof MW, Boulle A, Weigel R, et al. Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality. PLoS medicine **2009** Apr 28;6(4):e1000066.

116. Keiser O, Taffe P, Zwahlen M, et al. All cause mortality in the Swiss HIV Cohort Study from 1990 to 2001 in comparison with the Swiss population. AIDS (London, England) **2004** Sep 3;18(13):1835-43.

117. Jaggy C, von Overbeck J, Ledergerber B, et al. Mortality in the Swiss HIV Cohort Study (SHCS) and the Swiss general population. Lancet **2003** Sep 13;362(9387):877-8.

118. van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. AIDS (London, England) Jun 19;24(10):1527-35.

119. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. Annals of internal medicine **2007** Jan 16;146(2):87-95.

120. Gilks CF, Crowley S, Ekpini R, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet **2006** Aug 5;368(9534):505-10.

121. WHO. Scaling up antiretroviral therapy in resource-limited settings: guidelines for a public health approach. Executive summary. April 2002. IAPAC monthly **2002** Jun;8(6):168-75.

122. Mutevedzi PC, Lessells RJ, Heller T, Barnighausen T, Cooke GS, Newell ML. Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes? Bulletin of the World Health Organization Aug 1;88(8):593-600.

123. Bedelu M, Ford N, Hilderbrand K, Reuter H. Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care. The Journal of infectious diseases **2007** Dec 1;196 Suppl 3:S464-8.

124. Chan AK, Mateyu G, Jahn A, et al. Outcome assessment of decentralization of antiretroviral therapy provision in a rural district of Malawi using an integrated primary care model. Trop Med Int Health **2010** Jun;15 Suppl 1:90-7.

125. Loubiere S, Boyer S, Protopopescu C, et al. Decentralization of HIV care in Cameroon: increased access to antiretroviral treatment and associated persistent barriers. Health policy (Amsterdam, Netherlands) **2009** Oct;92(2-3):165-73.

126. Fetzer BC, Hosseinipour MC, Kamthuzi P, et al. Predictors for mortality and loss to follow-up among children receiving anti-retroviral therapy in Lilongwe, Malawi. Trop Med Int Health **2009** Aug;14(8):862-9.

127. Yang CH, Huang YF, Hsiao CF, et al. Trends of mortality and causes of death among HIV-infected patients in Taiwan, 1984-2005. HIV medicine **2008** Aug;9(7):535-43.

128. Collaboration C. Survival after introduction of HAART in people with known duration of HIV-1 infection. The CASCADE Collaboration. Concerted Action on SeroConversion to AIDS and Death in Europe. Lancet **2000** Apr 1;355(9210):1158-9.

129. Dorrucci M, Balducci M, Pezzotti P, Sinicco A, Alberici F, Rezza G. Temporal changes in the rate of progression to death among Italians with known date of HIV seroconversion: estimates of the population effect of treatment. Italian HIV Seroconversion Study (ISS). Journal of acquired immune deficiency syndromes (1999) **1999** Sep 1;22(1):65-70.

130. Correll PK, Law MG, McDonald AM, Cooper DA, Kaldor JM. HIV disease progression in Australia in the time of combination antiretroviral therapies. The Medical journal of Australia **1998** Nov 2;169(9):469-72.

131. Murphy EL, Collier AC, Kalish LA, et al. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. Annals of internal medicine **2001** Jul 3;135(1):17-26.

132. Vittinghoff E, Scheer S, O'Malley P, Colfax G, Holmberg SD, Buchbinder SP. Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. The Journal of infectious diseases **1999** Mar;179(3):717-20.

133. del Amo J, Perez-Hoyos S, Moreno A, et al. Trends in AIDS and mortality in HIV-infected subjects with hemophilia from 1985 to 2003: the competing risks for death between AIDS and liver disease. Journal of acquired immune deficiency syndromes (1999) **2006** Apr 15;41(5):624-31.

134. Zhang FJ, Pan J, Yu L, Wen Y, Zhao Y. Current progress of China's free ART program. Cell research **2005** Nov-Dec;15(11-12):877-82.

135. Zhang F. China Free Antiretroviral Therapy Manual, 2008 Edition. **2008**.

136. Ma Y, Zhang F, Zhao Y, et al. Cohort profile: the Chinese national free antiretroviral treatment cohort. International journal of epidemiology Aug;39(4):973-9.

137. Zhang F, Haberer JE, Wang Y, et al. The Chinese free antiretroviral treatment program: challenges and responses. AIDS (London, England) **2007** Dec;21 Suppl 8:S143-8.

138. Geng EH, Bangsberg DR, Musinguzi N, et al. Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. Journal of acquired immune deficiency syndromes (1999) **2010** Mar 1;53(3):405-11.

139. Zhang F, Dou Z, Ma Y, et al. Effect of earlier initiation of antiretroviral treatment and increased treatment coverage on HIV-related mortality in China: a national observational cohort study. The Lancet infectious diseases **2010** Jul;11(7):516-24.

140. Brinkhof MW, Dabis F, Myer L, et al. Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. Bulletin of the World Health Organization **2008** Jul;86(7):559-67.

141. Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PloS one **2009**;4(6):e5790.

142. Mugavero MJ, Norton WE, Saag MS. Health care system and policy factors influencing engagement in HIV medical care: piecing together the fragments of a fractured health care delivery system. Clin Infect Dis **2011** Jan 15;52 Suppl 2:S238-46.

143. Mugavero MJ, Lin HY, Willig JH, et al. Missed visits and mortality among patients establishing initial outpatient HIV treatment. Clin Infect Dis **2009** Jan 15;48(2):248-56.

144. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. The New England journal of medicine **2011** Aug 11;365(6):493-505.

145. UNAIDS. Report on the Global AIDS Epidemic Joint United Nations Programme on HIV/AIDS, Geneva **2010**.

146. China CSCAWCOaUTGoAi. A Joint Assessment of HIV/AIDS Prevention, Treatment, and Care in China: Beijing 2007. **2007**.

147. Zhang F, Dou Z, Yu L, et al. The effect of highly active antiretroviral therapy on mortality among HIV-infected former plasma donors in China. Clin Infect Dis **2008** Sep 15;47(6):825-33.

148. Dou Z, Chen RY, Wang Z, et al. HIV-infected former plasma donors in rural Central China: from infection to survival outcomes, 1985-2008. PloS one **2010**;5(10):e13737.

149. Ma Y, Zhang F, Zhao Y, et al. Cohort profile: the Chinese national free antiretroviral treatment cohort. International journal of epidemiology **2009** Aug;39(4):973-9.

150. Dou Z, Chen RY, Xu J, et al. Changing baseline characteristics among patients in the China National Free Antiretroviral Treatment Program, 2002-09. International journal of epidemiology **2010** Dec;39 Suppl 2:ii56-64.

151. Ekouevi DK, Balestre E, Ba-Gomis FO, et al. Low retention of HIV-infected patients on antiretroviral therapy in 11 clinical centres in West Africa. Trop Med Int Health **2010** Jun;15 Suppl 1:34-42.

152. Geng EH, Nash D, Kambugu A, et al. Retention in care among HIV-infected patients in resource-limited settings: emerging insights and new directions. Current HIV/AIDS reports **2010** Nov;7(4):234-44.

153. Liu J, Fan D. Hepatitis B in China. Lancet **2007** May 12;369(9573):1582-3.

154. Matthews G. The management of HIV and hepatitis B coinfection. Current opinion in infectious diseases **2007** Feb;20(1):16-21.

155. Liao L, Xing H, Shang H, et al. The prevalence of transmitted antiretroviral drug resistance in treatment-naive HIV-infected individuals in China. Journal of acquired immune deficiency syndromes (1999) **2010** Feb;53 Suppl 1:S10-4.

156. May MT, Sterne JA, Costagliola D, et al. HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis. Lancet **2006** Aug 5;368(9534):451-8.

157. Srikantiah P, Ghidinelli M, Bachani D, et al. Scale-up of national antiretroviral therapy programs: progress and challenges in the Asia Pacific region. AIDS (London, England) **2010** Sep;24 Suppl 3:S62-71.

158. Keiser O, Anastos K, Schechter M, et al. Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America. Trop Med Int Health **2008** Jul;13(7):870-9.

159. Cornell M, Grimsrud A, Fairall L, et al. Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002-2007. AIDS (London, England) **2010** Sep 10;24(14):2263-70.

160. Ewings FM, Bhaskaran K, McLean K, et al. Survival following HIV infection of a cohort followed up from seroconversion in the UK. AIDS (London, England) **2008** Jan 2;22(1):89-95.

161. Jensen-Fangel S, Pedersen L, Pedersen C, et al. Low mortality in HIV-infected patients starting highly active antiretroviral therapy: a comparison with the general population. AIDS (London, England) **2004** Jan 2;18(1):89-97.

162. Losina E, Schackman BR, Sadownik SN, et al. Racial and sex disparities in life expectancy losses among HIV-infected persons in the united states: impact of risk behavior, late initiation, and early discontinuation of antiretroviral therapy. Clin Infect Dis **2009** Nov 15;49(10):1570-8.

163. van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. AIDS (London, England) **2010** Jun 19;24(10):1527-35.

164. Ma Y, Zhao D, Yu L, et al. Predictors of virologic failure in HIV-1-infected adults receiving first-line antiretroviral therapy in 8 provinces in China. Clin Infect Dis Jan 15;50(2):264-71.

165. Hu Y, Zhou M, Wang L, et al. Analysis on characteristics of death patients in hospital in China, 2006. Disease Surveillance **2008**;23(12):788-91.

166. Rothman K, Greenland S. Modern Epidemiology, 2nd Edition. **1998**.

167. Zwahlen M, Harris R, May M, et al. Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries. International journal of epidemiology **2009** Dec;38(6):1624-33.

168. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. Clin Infect Dis **2010** Jun 1;50(11):1512-20.